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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

AUGUST, 1950

ORIGINAL ARTICLES

INFLUENCE OF ARTERIAL DISEASE ON THE SYSTOLIC BLOOD PRESSURE GRADIENTS OF THE EXTREMITY

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The proper diagnosis and treatment of many patients with peripheral arterial disease depend upon knowledge of the presence, location and extent of an arterial obstructing lesion. A partial obstruction of the arterial system results in a loss of energy which reflects itself as a pressure drop below an obstructed site. This pressure drop depends primarily upon the rate of blood flow and the cross sectional area of the stenosed artery at the site of the obstruction. It was felt that systolic pressures at various points on an extremity would give an insight into the presence, location and degree of arterial occlusion. It is the purpose of this report to describe a plethysmographic method of recording systolic blood pressures at various sites on an extremity and to describe the deviations of these blood pressures from normal among patients with various peripheral vascular disease states.

Methods and Materials. The systolic arterial pressure was determined using the Cambridge pneumo-plethysmograph.[1] A digital cup was sealed to the right or left second toe and right or left index finger using a non-constricting sealing material.[2] A ribbed-type blood pressure cuff was fastened, successively, to the thigh adjacent to the crotch, above the knee, below the knee, and at the ankle. A non-ribbed type sphygmomanometer cuff was wrapped around the foot in selected cases. The pressure within the occluding cuff was recorded using a mercury manometer. Blood pressure was determined from any site by inflating the cuff with sufficient air to obliterate the pulsation of the digit, as detected by the pneumo-plethysmograph. The air escape valve of the blood pressure cuff was cracked and the pressure within the cuff gradually reduced. The pressure in the manometer was noted when digital swelling began as signaled by an abrupt drift of the plethysmographic string. The end point was clearly defined among patients who did not show a high degree of vasoconstriction. All determinations were made with subjects dressed in a hospital gown, resting on a horizontal bed, covered with 1 light wool blanket.[3] Determinations were made after a 60-minute rest at a room temperature of 25° C. ± 1.5. The blood pressures from the 5 sites of the lower extremities and comparable points on the upper extremities, were determined in 10 normal individuals and 25 patients with arterial disease. The diseased group included patients with arteriosclerosis obliterans, thromboangiitis obliterans, arterial embolism and periarteritis nodosa.

Results. 1. Comparison of the Plethysmographic and Auscultatory Techniques for Recording Systolic Arterial Blood Pressures. The relationship between the antecubital systolic pressures obtained using the auscultatory technique and the plethysmographic technique is shown in Fig. 1. Twenty-five determinations were made on a total of 6 normal individuals and

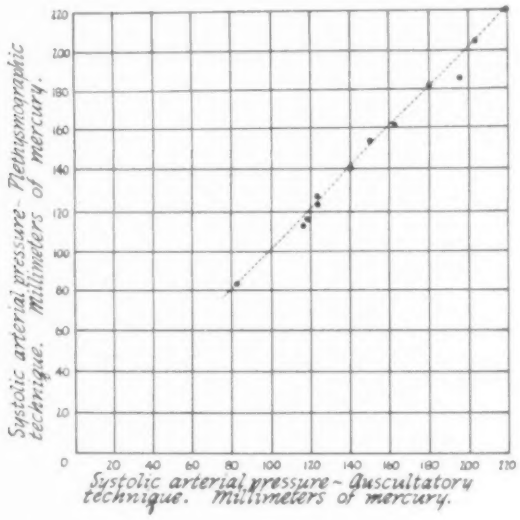

FIG. 1.—The relationship between systolic antecubital arterial blood pressures, using the auscultatory and plethysmographic methods.

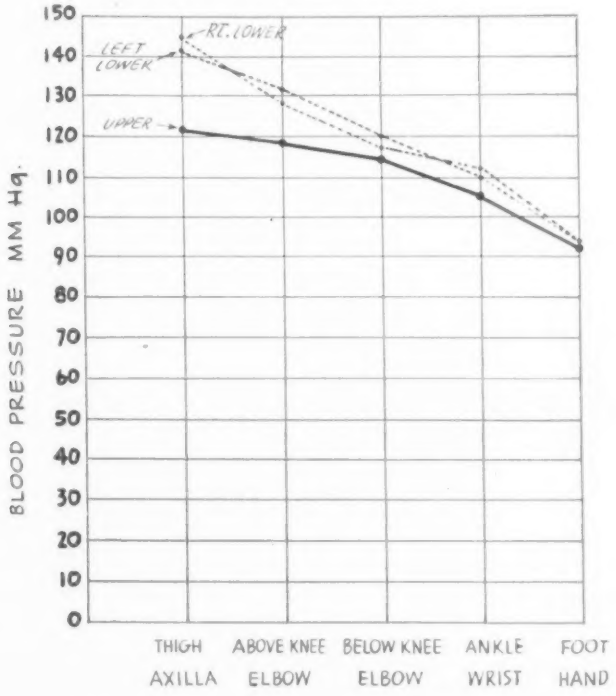

FIG. 2.—Normal blood pressure gradients of the upper and lower extremities.

6 patients with arteriosclerotic obliterative disease. There was a mean difference between the 2 methods of 1.2 mm. Hg. The greatest difference was 8.0 mm. The coefficient of correlation was 0.997. The correlation was good at high, medium and low pressures.

2. Blood Pressure Gradients Higher in the Lower Extremities than in the Upper Extremity (Normal). Blood pressure gradients were studied in one upper extremity and both lower extremities in 10 normal individuals (Fig. 2). Six males and 4 females were studied. The average was 24 years (range 18 to 30). In all instances the blood pressures were higher on all points of the lower extremity than on comparable points of the upper[5]. The pressures at the thigh and axilla were highest and decreased toward the periphery. The mean values for right and left lower extremities for the thigh, above the knee, below the knee, ankle and foot were 143, 130, 119, 111, and 94. The pressures between these points differed by 13, 11, 8, and 17 mm. Hg. respectively. The pressure drop from thigh to foot was 49 mm. Hg. and from thigh to ankle 32 mm. The pressures of the upper extremity at the axilla, above the elbow, below the elbow, at the wrist and palm were 121, 118, 114, 105 and 92 mm. of mercury. The differences beteen these pressures beginning at the axilla, were 3, 4, 9, and 13 mm. respectively. The pressure drop from axilla to palm was 29 mm. and from axilla to wrist 16 mm. The pressure at the thigh was 22 mm. Hg. higher than at the axilla. That above the knee was 12 mm. above the measurement above the elbow. The pressure below the knee was 5 mm. above that below the elbow and that at the ankle as 6 mm. above the pressure at wrist. The pressure of the foot was 2 mm. above the palm. The blood pressure index at any point $\frac{\text{blood pressure of lower extremity}}{\text{blood pressure of upper extremity}}$ was in all instances greater than 1.

3. Blood Pressure Gradients of Lower Extremities Below Those of Upper Extremity. Gradients of this type were encountered in 24% of patients with arterial disease in this study. In all instances arteriosclerosis obliterans which involved the lower portion of the aorta and iliac arteries was present. The Leriche syndrome[3] was present in all patients. Fig. 3 shows the blood pressure gradients of a 39-year old male who complained, for the past 4 years, of "tiredness" of the thighs and calves on walking one block. The blood pressure gradients of the lower extremities were lower than those of the upper extremity. The pressure at the axilla was 128, at the left thigh 112, and at the right thigh 100 mm. Hg. The pressure drops from thighs to below the knees were greater than normal and the drops from below the knees to the feet were less than normal. These gradients were interpreted as indicating obstruction of the aorta, iliac, femoral and popliteal arteries. Roentgenograms of the lumbar region showed calcification of the lower portion of the aorta and iliac arteries with definite narrowing at at the bifurcation of the aorta. Auscultation of the abdomen, below the umbilicus, revealed a Grade III systolic murmur but no thrill. No cardiac murmurs were present. Femoral arterial pulsations were questionable. No pulsations could be felt in the popliteal, posterior tibial or dorsalis pedis arteries. No tissue changes were evident in the feet. During a lumbar sympathectomy the aorta and right iliac arteries were palpated and found to be firm, small and non-pulsating. A thrill was felt along the lower portion of the aorta and left iliac artery. A needle was placed into the aorta and a trickle of

blood under low pressure was aspirated.

4. Blood Pressure Gradients Lower in One Lower Extremity than in the Upper Extremity. This occurred in 24% of patients with arterial disease in this series. A typical case is shown in Fig. 4. The blood pressure at the right thigh was 150, at the axilla 140 and at the left thigh 133 mm. Hg. The pressure drop from the left thigh to below the left knee was greater than normal. These findings were interpreted to indicate the presence of an obstructing lesion of the left iliac, femoral and popliteal arteries. The patient, a 45-year old male, sustained a gunshot wound in the popliteal region 30 years ago. This was followed by an A-V fistula, surgical repair, and subsequent popliteal and femoral arterial thrombosis. Examination revealed normal pulsations of the right femoral, popliteal, posterior tibial and dorsalis pedis arteries. On the left, the pulsations of these arteries could not be detected. A large, firm, non-pulsating mass was felt in the left popliteal region. During a left lumbar sympathectomy the left iliac artery was noted to be firm and non-pulsating. No blood could be aspirated from the distal portion of this artery.

5. Blood Pressures of Ankles and Feet Below those of Wrist and Hand with Thigh-Axillary Relationship (Normal). This distribution of arterial disease occurred in 20% of patients in this series. The gradients in Fig. 5 are the findings of a 63-year old diabetic female who entered because of increasing pain in the right ankle of 3 days' duration. The blood pressure at the hand was 120, while those of the left and right feet were 54 and 40 mm. Hg. respectively. The blood pressures of the lower extremities were essentially normal at the level of the thigh, above the knee and below the knee with a sharp drop of the pressures at the ankles and feet. These findings were interpreted as indicating the presence of obstructive lesions involving the tibial and, or, peroneal arteries bilaterally. Temperature 102° F. The right ankle and foot were red, hot and swollen. Moderate pulsations of the femoral and popliteal arteries were present. Posterior tibial and dorsalis pedis pulsations were absent bilaterally. Because of a rising temperature and ascending cellulitis of the right leg, a right supracondylar amputation was performed. Free bleeding from the proximal arteries was encountered during the surgical procedure. Dissection of the arteries of the amputated limb revealed high grade obstruction of the distal portions of the tibial and peroneal arteries as a result of atheromatous and calcific plaques.

Discussion. The systolic blood pressure was easily determined at various points on an extremity by the plethysmographic method, and the results correlated well with the auscultatory method when checked at the antebrachium. The pressure which is recorded from the occluding cuff at the first detectable increase in volume of the digit is the approximate arterial pressure under the occluding cuff regardless of its position on the extremity. The swelling of the digit is merely a signal which announces the time when the pressure within the artery has just overcome the pressure within the occluding cuff. The relationship between the width of the cuff and the volume of the part is important in determining the blood pressure by an occluding method such as this. Attempts to measure the blood pressure of a part as small as a digit demonstrated the variation in the pressure obtained depending upon the width of the cuff employed. In order to reduce the number of variables in these experiments a

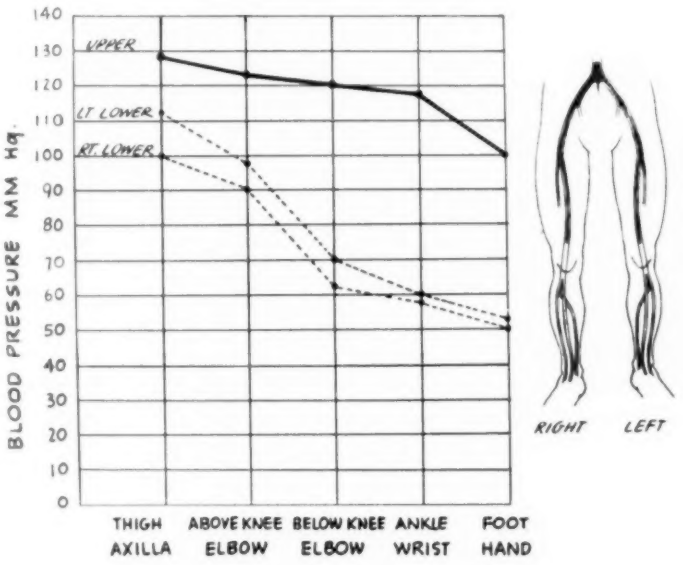

FIG. 3.—Blood pressure gradients of the upper and lower extremities in a patient with chronic arteriosclerotic obliterative disease of the lower portion of the aorta and iliac arteries.

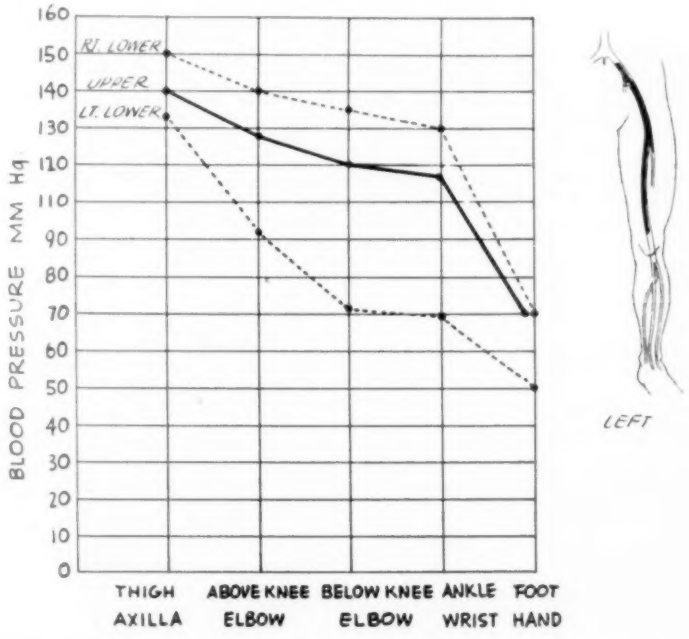

FIG. 4.—Pressure gradients from a patient with thrombosis and obstruction of the left iliac, femoral, and popliteal arteries.

standard 13 cm. cuff was employed at all points regardless of the size of the part.

An analysis of the normal pressure gradients and their variations in different disease states made possible the selection of a group of curves typical of various conditions (Figs. 2 to 5 and 9).

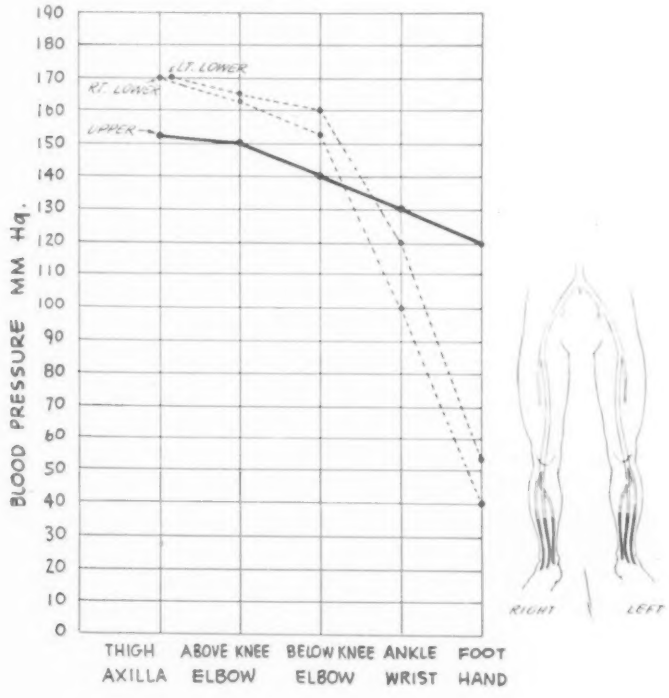

FIG. 5.—Pressure gradients in the upper and lower extremities of a patient with arteriosclerosis obliterans of the distal portions of the tibial and peroneal arteries bilaterally.

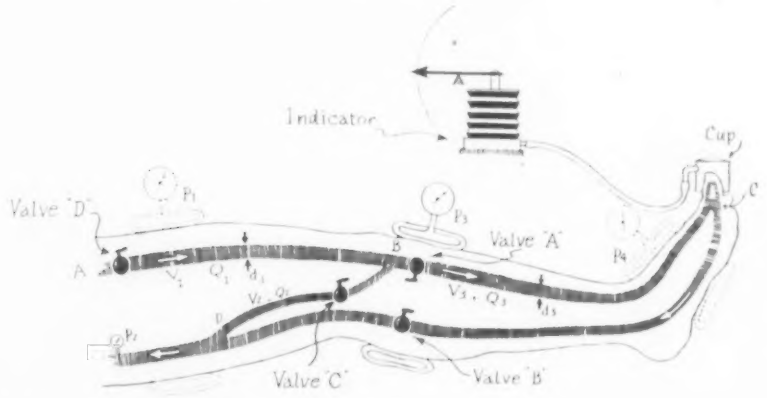

FIG. 6.—Schematic representation of the method of measuring blood pressure using the pneumo-plethysmograph (see text for explanation).

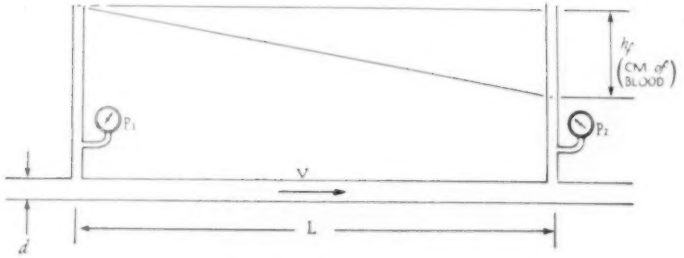

FIG. 7.—Schematic diagram showing a pressure drop as a result of fluid flow through a vessel (see text for explanation).

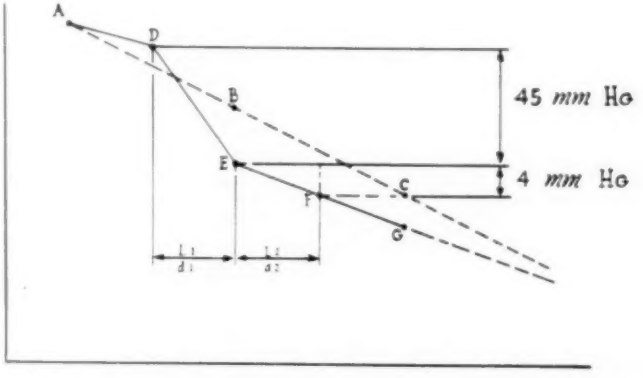

FIG. 8.—Determination of approximate size of an obstruction in the arterial system of the lower extremity. A normal blood pressure gradient is shown by the line A-B-C. An abnormal gradient is shown by the line A-D-E-F-G. A—represents the blood pressure taken at the thigh, D—above the knee, E—below the knee, F—at the ankle and G—at the foot.

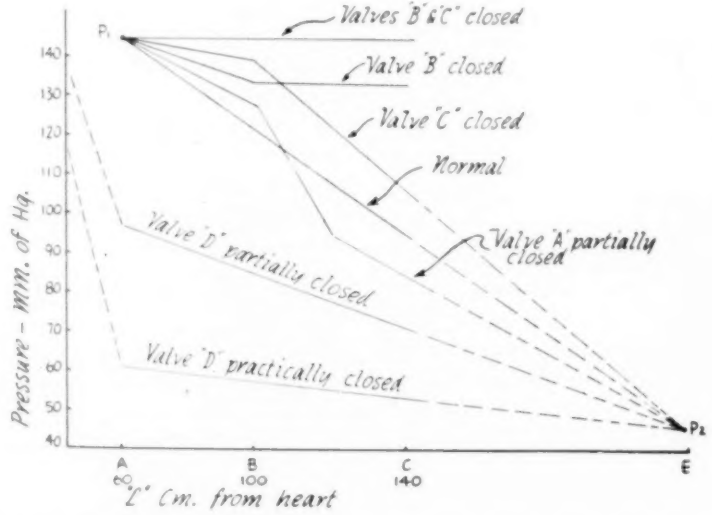

FIG. 9.—A theoretic family of blood pressure gradients which were derived from the possibilities depicted in Figure 6 (see text for explanation).

An obstructing lesion below the thigh, knee, calf, or ankle resulted in a marked pressure drop just beyond the obstructed site. Among normal individuals the pressures in the lower extremities were higher at all points than those in the upper. Aortic obstruction was characterized by blood pressures which were lower in the lower extremities than in the upper extremity at all comparable points. Obstruction of an iliac artery showed pressures which were lower at all points on the obstructed side than on the unobstructed side. The pressures on the obstructed limb were below those of the upper extremity while the pressures of the unobstructed limb were above those of the upper extremity. Femoral arterial obstruction produced normal or slightly elevated pressures at the thigh and lower pressures above the knee on the diseased side. The gradient from this point to the periphery tended to be flat. Popliteal arterial obstruction was characterized by normal or slightly elevated pressures at the thigh and above the knee with a high degree pressure drop below the knee. From this point to the foot the pressure drop was slight. Tibial and peroneal obstruction was characterized by relatively normal pressures at the thigh, above the knee and below the knee. The pressure drop from below the knee to the ankle was great. With extensive arterial disease resulting from stenosis of a long segment of the arterial system, the pressure drop from thigh to foot was great. With intermittent vasospasm the pressures often varied rapidly, giving a saw-toothed gradient. In the presence of diminished blood flow due to any cause, the pressure drop between points was diminished. With hypertension, the pressure at the thigh was high and the pressure drop between points was great. Decrease of the pressure in one leg usually indicated disease on that side; however, in a patient with multiple congenital arteriovenous fistulae on the left side the pressures on the left extremity averaged 20 mm. Hg. higher at all points than on the right.

The changes in pressure at the various sites can be analyzed employing Bernoulli's principle. Differences in pressure may result from a shunting of blood from artery to vein, from differences in size in arteries, from turbulences set up because of differences of anatomic structures, from differences in flow rates which come about because of obstruction of the vessel, and other factors.

Measurements of the blood pressure of the lower extremities at the above mentioned sites may reflect the hydrostatic pressure which exists between the heart and the occluding cuff and probably does not represent the exact pressure which exists in the arterial system when an occluding cuff is not in place. Thus, there may be differences in the values obtained between an occluding method where end pressure is measured and a direct method where intraluminal pressures are measured.

In these experiments the blood pressure gradients were recorded with the subject in the supine position. The bed was maintained in a horizontal position as checked with a level. Deviations from the horizontal caused changes in the pressure gradients which could be accounted for on the basis of gravity and reflex vasoconstriction. When the foot of the bed was depressed slightly the differences in blood pressure at the various points on the extremities could ordinarily be accounted for on the basis of gravity. With the patient in the vertical position gravity alone could not explain the altered pressures which probably resulted in large part from arteriolar constriction. Such vasomotor reflexes probably serve as check valves which tend to prevent undue pressure on the frail walls of the capillary bed.

Mathematical Considerations: *Technique of measuring pressures**. The fluid pressure at any point in the leg from the thigh to the foot is measured by placing a cuff at a point such as P_3 (Fig. 6) and increasing the pressure until the flow is stopped in the artery below the cuff. The pressure is slowly released until the indicator (plethysmographic string shadow) shows a deflection and, at this time, the cuff pressure is recorded. Such a reading is taken as if Valve B were closed and Valve A partially open. The blood pressure within the toe will be sufficient to cause a swelling of the toe resulting in a movement of the indicator. With Valve B closed the flow Q_3 must be zero; therefore, assuming P_1 is constant, the resultant drop in flow of Q_2 causes the friction loss to be less than normal. Thus, pressure recorded at P_3 must be slightly higher than the result obtained by a direct measurement.

Blood pressure readings at the arm remain constant before and after tourniquets are applied first to one thigh, then to both thighs. This test shows that the pressure at P_1 will remain constant even when the circulation as represented by Q_1 is reduced or completely shut off. The error first mentioned, due to change in flow conditions, is offset by the error due to elastic forces of the vessels and tissues so that pressure readings by an occluding method should give a pressure gradient very close to the true pressures obtained by a direct method.

If the blood velocity and diameter of the vessel are known, it is possible to determine whether or not the flow is laminar or turbulent by Reynolds Number, R_e. $R_e = \frac{Vd}{\nu} = \frac{Vd}{.02}$. If Reynolds Number is over 2000 the flow is probably turbulent. In the aorta the velocity is about 40 cm./sec. and the diameter about 2 cm. $R_e = \frac{40 \times 2}{.02} = 4000$. Thus, the flow in this portion of the circulatory system may be turbulent.

Assuming that the velocity in the artery of a normal person from above to below the knee is 100 cm./sec., L = 20 cm., d = 3 mm., then $R_e = \frac{100 \times 0.3}{.02} = 1500$. Therefore the flow is laminar and $h_f = \frac{32\nu LV}{gd^2} = \frac{32 \times .02 \times 20 \times 100}{980 \times .09} = 14.4$ cm., or h_f is about 10 mm. Hg, which has been found to be about a normal gradient.

Determination of the Size of an Obstruction. For a normal person the pressure gradient in the leg is represented by the gradient A–B–C, (Fig. 8). An abnormal leg is represented by A–D–E–F–G. The steep drop D–E cannot be explained by normal friction loss and is probably caused by an obstruction. It is possible to make an estimate of the orifice diameter. It can be shown that the velocity through an orifice is $V = 0.65 \times (2g \triangle h)^{\frac{1}{2}}$, provided the ratio of orifice diameter to artery diameter is less than 0.4. Using values from Fig. 8: $V = 0.65 \times (2 \times 980 \times 63)^{\frac{1}{2}} = 230$ cm./sec.

We now know the velocity through the orifice, but to find the diameter we must ascertain the velocity in section E–F. As the drop is less than normal, we can use the friction loss relation for laminar flow assuming d = 2 mm.

$V_2 = \frac{h_f g d^2}{32\nu L} = \frac{5.6 \times 980 \times .04}{32 \times .02 \times 20} = 17.2$ cm./sec.

Thus, the velocity in section E–F is 17.2 cm./sec. By the relation $\frac{V_1}{V_2} = \frac{d_2^2}{d_1^2}$ we can find the orifice diameter $\frac{230}{17.2} = \frac{.04}{d_1^2}$ or $d_1^2 = .003$ or $d_1 = .055$ cm., or

* A = cross-sectional area of artery or vein — cm^2
d = diameter of artery, vein or orifice — cm
f = friction factor for pipes — dimensionless
g = acceleration of gravity = 980 — cm/sec^2
H = total effective head — cm of blood
h = any head — cm of blood
h_f = head lost in friction — cm of blood
$\triangle h$ = a differential head — cm of blood
K = any constant
L = length of artery or vein — cm
n = any abstract number
P = pressure — mm of Hg
Q = rate of discharge — cm^3/sec
Re = Reynolds number — dimensionless
V = mean velocity of blood — cm/sec
μ = kinematic viscosity (Nu) — cm^2/sec

Normal Friction Losses. In a normal person the pressure drop, (P_1-P_2) (Fig. 7) for a given length, L, of an artery or vein of a diameter, d, will be due to friction loss. In general the flow in an artery will be laminar or viscous. If this condition is true, the loss, h_f, will be due to fluid shear stress and the frictional loss will be independent of the roughness of the artery wall.

The loss due to laminar flow can be shown to be $h_f = \frac{32\nu LV}{gd^2}$.

Frictional loss due to turbulence is possible in some of the larger arteries, in which case $h_f = \frac{f\,L\,V^2}{d\,2g}$. "f" is dimensionless and its value depends on the roughness of the artery.

the orifice diameter in the obstruction is about 0.5 mm.

Interpretation of Typical Curves. Two fundamental relations apply to the flow as indicated in Fig. 6. First, the flow, Q_1, through A–B must always equal the sum of the flow, Q_2, through B–D and the flow, Q_3, through B–C–D. Second, the head loss through B–D equals that through B–C–D. In this particular problem, we assume that the total head available, P_1-P_2, is always constant.

The loss of head in any section may be written $h_f = K\frac{V^2}{2g}$ or $V = \frac{1}{K}(2gh_f)^{\frac{1}{2}}$ as $Q = VA$ and as we can assume the cross sectional area, A, of the artery or veins as constant, it follows that $Q_1 = K_1'(h_1)^{\frac{1}{2}}$, $Q_2 = K_2'(h_2)^{\frac{1}{2}}$, $Q_3 = K_3'(h_3)^{\frac{1}{2}}$ but $h_2 = h_3$ and $Q_1 = Q_2 + Q_3$, therefore $K_1'(h_1)^{\frac{1}{2}} = (K_2' + K_3')(h_2)^{\frac{1}{2}}$ *1*

$$P_1 - P_2 = H = h_1 + h_2 \qquad 2$$

If valve A is partially closed and the other valves are open, then K_3' becomes smaller. In order to satisfy relations *1* and *2* h_2 and Q_2 must then become larger while h_1 and Q_1 will be smaller.

In the same manner, an analysis of the flow conditions can be made with other combinations of closed or partially closed valves. Fig. 9 graphically shows some of the possible combinations.

Summary. Systolic arterial pressure gradients of the upper and lower extremities were studied in normal individuals and patients with organic occlusive arterial disease.

Differences in gradients were determined among normal and abnormal individuals. Normal individuals showed a thigh to toe pressure drop of 49 mm. Hg. with a groin to knee, knee to calf, calf to ankle, ankle to foot falls averaging 12.5 mm. Hg.

In the presence of arterial obstruction, of either an organic or spastic nature, there was a marked pressure drop distal to the site of the obstruction amounting to as much as 50 or 60 mm. Hg. The position of the pressure drop in the curve indicated the approximate site of the obstructing lesion.

In the presence of extensive arterial disease involving the iliac artery and distal arterial segments, the thigh pressure was lower on the diseased side than on the intact side and the thigh to foot pressure drop was greater than normal. With disease of the iliac artery, the thigh pressure was low; however, the thigh to foot drop was somewhat flat. Disease of the femoral artery produced a marked pressure drop detected above the knee. Popliteal arterial obstruction produced a blood pressure drop which was marked below the knee. Tibial-peroneal obstruction produced a pressure drop which was marked at the ankle.

Intermittent vasospasm produced variations of pressures which gave a peaked type of gradient. Diminished flow was characterized by a diminished increment of pressure between blood pressure points.

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REFERENCES

1. **Burch, G. E.**: Am. Heart J., **33**, 47, 1947.
2. **Goetz, R. H.**: Ibid., **31**, 146, 1946.
3. **Leriche, R.**: Presse med., **48**, 601, 1940.
4. **Neumann, C., Cohn, A. E.,** and **Burch, G. E.**: J. Clin. Invest., **21**, 651, 1942.
5. **Wendkos, M. H.,** and **Rossman, P. L.**: Am. Heart J., **26**, 623, 1943.

THE TREATMENT OF ANGINA PECTORIS WITH A PREPARATION OF KHELLIN (AMMI VISNAGA)*

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Khellin (2-methyl-5, 8-dimethoxy-furanochromone) is one of the 3 active crystalline substances that has been isolated from the fruit of Ammi Visnaga, a plant which grows wild in the eastern Mediterranean countries. In 1932, Samaan[10] studied the pharmacological action of this principle and found that it caused relaxation of all smooth muscle by its direct action on the muscle fibers. Anrep *et al.*[1] investigated the coronary dilating effect of khellin in the heart-lung preparation and in the intact animal. They observed that with concentrations of 1 in 200,000 the coronary blood flow increased 3 to 4 times. No effect on the systemic blood pressure was noted unless the drug was injected very rapidly, and the fall that did occur was only transient. In their opinion, the drug had a selective action on the coronary vessels and a more prolonged action than that of the nitrites. Khellin is rapidly absorbed after intramuscular injection, reaching its maximum concentration in the blood stream in about 5 minutes and remaining there for as long as 24 hours to 5 days. Absorption from the alimentary tract is also relatively rapid, the peak level being obtained in 10 to 30 minutes. After absorption the drug is distributed throughout all tissues and its disappearance is slow[5]. Due to this long retention of the drug in the blood and tissues a cumulative effect occurs.

In 1945, Kenawy and Barsoum[8] first reported the use of khellin in the treatment of angina pectoris*. They treated 7 cases and thought that results were promising. Anrep *et al.*[1] used the drug in 38 cases of angina pectoris with improvement in 35 and Ayad[4] reported 83% improvement in 23 cases. The largest clinical study to date has been the report of 250 cases of angina pectoris by Anrep *et al.*[2] in 1949. Ninety per cent of these 250 showed improvement. In view of such encouraging results, it was thought that further study of the effect of khellin in angina pectoris was desirable.

Material and Methods. Fifty-three patients with a classical history of angina pectoris were studied. The patients were divided into 2 groups. Group 1 consisted of 28 patients studied in the Out-Patient Clinic of the Peter Bent Brigham Hospital. There were 17 males and 11 females, varying in age from 44 to 77 years with an average age of 60

* This study was aided by a grant from the Smith, Kline & French Laboratories, Philadelphia, Pa.

* In almost all reports, "Khellin" has been used to designate a mixture consisting of 70-80% Khellin and 20-30% visnagin (2-methyl-5-methoxyfuranochromone) which is said to have about 60% the biological activity of pure Khellin[3]; it will be so used in this paper.

years. The duration of the angina pectoris varied from 2 months to 16 years, and was greater than 2 years in 16 patients. Seven patients had what was regarded as mild angina pectoris (seven or fewer episodes of pain per week), 17 moderately severe (up to 30 episodes of pain per week with occasional attacks at rest), and 4 patients had severe angina pectoris (as many as 150 episodes per week with numerous spells at rest). We are aware that this is a purely arbitrary classification and that there is no simple way of grading the severity or seriousness of angina. All patients received a routine physical examination, Roentgenograms of the chest and electrocardiograms consisting of the 3 standard limb leads, 3 augmented unipolar limb leads and 6 precordial leads (V). Eight patients had normal electrocardiograms, 13 showed the pattern of left ventricular hypertrophy (3 of these in addition had evidence of an old myocardial infarction), 1 showed incomplete right bundle branch block, and 2 had left bundle branch block. Nineteen patients had an exercise tolerance test as described by Master[9] before therapy was started. Thirteen of these tests were taken as positive, *i.e.*, electrocardiographic changes were present. Six patients had the test repeated after a course of treatment; the results are considered later. Twenty-four patients were observed for periods of from 1 to 8 months. Four were studied for 3 weeks or less because of their refusal to continue treatment. During the time of observation the patients were maintained alternately on periods of khellin medication and of placebo medication, each from 3 to 10 weeks in duration. Neither the individual under study nor the observers knew whether the preparation being used was placebo or khellin. Early in the study the placebos and the drug were not identical in appearance but at some time during the subsequent observations all patients received placebos identical to khellin in all appearances. The patients were seen at intervals of 1 to 3 weeks during the entire period of observation.

Group 2 consisted of 25 cases treated in the office practice of one of us (S. A. L.) for periods of 7 days to 2 weeks. There were 19 males and 6 females, varying in age from 44 to 76 years, with an average age of 57 years. The duration of the angina pectoris varied from 1 to 14 years. No exercise tolerance tests were performed and no placebos were used.

Each patient of both groups kept a written record of the number of nitroglycerin tablets used and the number of anginal attacks per week while under observation. They were encouraged to carry on their ordinary activities. Khellin was administered by mouth to each patient, (in the form of "Eskel" tablets*, 40 mgs. t.i.d.)** after meals or with meals. In some patients the dose was increased to 4 times daily or decreased to once or twice daily depending on whether or not side effects developed.

TABLE 1.—RESULTS OF KHELLIN THERAPY

	Results		
Severity of Angina Pectoris	*Definite improvement*	*Slight improvement*	*No improvement*
Group 1			
Mild	1	3	3
Moderate	5	5	7
Severe	2		2
			No improvement
Group 2	*Improvement*		
	13		12
Total	29		24

Results of Treatment. Khellin was judged to be of definite value when the number of episodes of angina pectoris or the number of nitroglycerin tablets used per week was 50% or less than when on placebo therapy, of slight value when the number was only slightly less than when on placebo treatment, and of no value when the placebo effect was equal to or better than the drug results. The results are summarized in Table 1 and the details of the individual cases in Table 2. It may be seen that improvement was

* Supplied by Smith, Kline & French Laboratories. This product, like those used in previous studies, is a mixture consisting approximately of Khellin 75% and visnagin (when assayed as Khellin equivalent) 25%.

** In most earlier reports the dosage is given in 50 mg. units. It should be noted, however, that at that time the Khellin and Khellin equivalent (visnagin) were estimated by inexact calorimetric methods; more precise assays, by recently developed methods, indicate that the "50 mg." tablets actually contain 40 mg. of active principle.

TABLE 2.—DATA ON INDIVIDUAL CASES

GROUP I. FROM HOSPITAL OUT PATIENT CLINIC

No.	Age	Sex	Duration Angina Pectoris	Severity Angina Pectoris	Aver. Nitrogly. Tablets per week: Before Rx	Placebo Rx	Khellin Rx	Patients Impression	Duration Observation	Side Effects	Result
1	50	M	10 yrs.	Mild	3-4	3-4	2-3	Attacks milder Walks better	6 mo.	Nausea, dizziness Drug rash	Slight imp.
2	62	F	2 yrs.	Mod.	21-28	7-21	2-4	Attacks milder Walks better	5 mo.	Nausea, anorexia, dizziness	Definite imp.
3	60	F	2 mo.	Mod.	21-28	0-2	0	Attacks milder Walks better	7 mo.	Nausea, anorexia insomnia	Slight imp.
4	53	F	9 mo.	Mild	6-7	6-7	—	No value	2 mo.	Nausea, vomiting, dizziness	No value Refused drug
5	63	M	5 yrs.	Mod.	7-14	10-15	7-10	Attacks milder Walks better	7 mo.	None	Slight imp.
6	58	M	9 yrs.	Severe	125-150	50-75	25-35	Fewer attacks	4 mo.	None	Definite imp.
7	65	M	6 yrs.	Mod.	28-42	50-70	7-14	Walks better	6 mo.?	None	Definite imp.
8	58	M	1.5 yrs.	Mod.	3-4	5-7	1	Helpful	7 mo.	Nausea, anorexia	Definite imp.
9	68	M	6.5 yrs.	Mod.	30-35	15-20	20-25	Helpful	7 mo.	Nausea, dizziness	No. imp.
10	55	M	10 mo.	Mild	5-7	4-7	0-2	Fewer attacks	3.5 mo.	None	Slight imp.
11	71	M	16 yrs.	Mod.	15-20	7-14	1-2	Very helpful Walks better	4.5 mo.	Nausea, anorexia Drug rash	Definite imp.
12	60	M	1 yr.	Mild	3-5	0-2	0-1	Helpful	4.5 mo.	None	No. imp.
13	53	M	1.5 yrs.	Mild	2-3	1-3	1-3	No help	2 mo.	None	No imp.
14	68	F	2 yrs.	Mod.	7-10	7-9	3-5	Helpful	4 mo.	Anorexia, insomnia	Slight imp.
15	60	M	6 yrs.	Mod.	7-14	0-2	0-1	Walks better	4 mo.	None	No imp.
16	50	F	5 yrs.	Mod.	10-14	—	4-8	Less pain	3 mo.	Nausea, dizziness, vomiting	Slight imp.
17	63	M	4 yrs.	Mild	2-4	2-4	0	No pain Walks better	2 mo.	None	Definite imp.
18	55	M	6.5 yrs.	Mild	5-10	4-6	0-3	Less pain	3.5 mo.	Nausea, anorexia	Slight imp.
19	60	M	1 yr.	Severe	75-100	30-46	10-18	Helpful	7 mo.	Nausea	Definite imp.
20	77	F	17 yrs.	Mod.	14-21	5-15	9-16	No help	3 mo.	Nausea, anorexia dizziness	No imp.
21	44	F	1.5 yrs.	Mod.	20-25	5-10	6-15	Helpful	3 mo.	Nausea, anorexia, dizziness	No imp.
22	63	F	10 mo.	Mod.	21-28	1-7	0-1	Too sick	2 mo.	Nausea, anorexia, dizziness	Slight imp.
23	58	M	4 yrs.	Mod.	10-15	7-15	—	Refused further Rx	1 mo.	Nausea, anorexia, dizziness	No imp.
24	75	F	12 yrs.	Mod.	20-25	20-25	2-5	Great help	8 mo.	Nausea, anorexia	Definite imp.
25	63	M	3 wks.	Severe	20-30	—	—	Refused further Rx	2 wks.	Nausea	No imp.
26	60	F	6 yrs.	Severe	4-50	—	—	Refused further Rx	2 wks.	Nausea, anorexia	No imp.
27	72	M	1 yr.	Mod.	20-30	—	—	Refused further Rx	1 wk.	Nausea, anorexia, dizziness	No imp.
28	60	F	1 yr.	Mod.	14-28	—	15-20	Helpful	3 wks.	None	Died
29	76	M	12 yrs.					Definitely helpful		Nausea	imp.
30	62	M	7 yrs					Definite help		Nausea, dizziness	Imp.
31	45	M	14 yrs.					No help		None	No Imp
32	61	M	2 yrs.					No help		None	No imp.
33	60	M	5 yrs.					No help		None	No imp.
34	44	M	10 yrs.					Pain milder Helpful		None	Imp.
35	76	F	4 yrs					No help		Nausea, anorexia	No imp.

No.	Age	Sex	Duration Angina Pectoris	Severity Angina Pectoris	Aver. Nitrogly. Tablets per week: Before Rx	Aver. Nitrogly. Tablets per week: Placebo Rx	Aver. Nitrogly. Tablets per week: Khellin Rx	Patients Impression	Duration Observation	Side Effects	Result
36	55	M	2 yrs.					Definite help		Nausea	Imp.
37	55	M	1 yr.					Slight help		Nausea	Imp.
38	49	M	5 yrs.					Helpful		Nausea, dizziness	Imp.
39	57	M	7 yrs.					No help		Nausea, anorexia	No imp.
40	56	M	1 yr.					No help		None	No imp.
41	49	M	3 yrs.					No help		Nausea, dizziness	No imp.
42		M						No help		Nausea	No imp.
43	49	F	3 yrs.					No help		None	No imp.
44	62	F	1 yr.					No help		Dizziness, insomnia	No imp.
45	46	M	1 yr.					Definite help		None	Imp.
46	52	F	5 yrs.					Slight help		Nausea, Dizziness	Imp.
47	56	M	1 yr.					Helpful		Nausea	Imp.
48	46	M	2 yrs.					Helpful		None	Imp.
49	66	F	4 yrs.					No help		Insomnia	No imp.
50	62	F	1 yr.					No help		Nausea	No imp.
51		M	1.4 yr.					Helpful		Nausea	Imp.
52	69	M	2 yrs.					Helpful		Insomnia	Imp.
53	54	M	3.5 yrs.					Helpful		None	Imp.

noted in 16 (57%) of 28 patients in Group 1. In 3 cases in which the drug was judged to be of no value, the trial was 3 weeks or less in each. It was discontinued because of side effects. Six patients who, before therapy, had positive electrocardiographic changes on exercise had this test repeated after a course of treatment. In 4 the same electrocardiographic changes took place on exercise but the pain that they had previously experienced did not develop. The other 2, who had no pain on the exercise test, had the same electrocardiographic changes before and after treatment.

The patients' opinion as to the value of the drug was also analyzed. Nineteen (68%) of the 28 patients said that the drug was helpful. They stated that they were having fewer episodes of pain, and, more particularly, that when the pain did occur it was of a milder nature. The ability to walk greater distances than prior to treatment was mentioned by many, *i.e.*, their exercise tolerance was increased. There were only 3 cases of the 19 who said they were better who did just as well on placebos. In the other 16 cases the subjective improvement which the patient ascribed to the khellin disappeared when placebo therapy was again instituted.

Thirteen (52%) of Group 2 patients stated that the drug was helpful in that they had less pain, used fewer nitroglycerin tablets and could walk longer distances.

When factors such as age, sex, hypertension and duration of angina were considered for both groups, there was nothing to suggest that any particular type of patient responded any better than another.

Side Effects. Nineteen (68%) of the patients in Group 1 complained of untoward effects. The most common and troublesome of these were anorexia, nausea and dizziness. In many patients the nausea and loss of appetite was not distressing enough for them to discontinue the drug completely but was bothersome, and some took the

drug irregularly. Nausea occurred in 18 of the 28 cases, anorexia in 15 cases and dizziness in 10 cases. In 5 patients the symptoms were so severe that they refused any further therapy. In several, dizziness was so serious that they were unable to continue their activities and had to remain in bed, 2 refusing further treatment. Insomnia developed in several but was severe in only 1 case. Two patients developed a maculopapular rash. The rash required approximately 3 weeks to disappear and reappeared when the drug was administered again. All of these side effects developed on dosages of 120 mg. daily. Twenty-one patients were able to continue the drug if the dosage was lowered to 40 or 80 mg. per day or continued in spite of the side effects. Seven were unable to take the drug at any level of dosage.

Fourteen (56%) in Group 2 of the 25 patients complained of nausea, anorexia and dizziness. The development of these untoward side-effects did not seem to influence the response of the patient to the drug, except where the drug had to be discontinued.

Discussion. The evaluation of the efficacy of any drug in the treatment of angina pectoris is fraught with many difficulties, as is well known. Symptoms often spontaneously go through cycles of exacerbation and remission without adequate explanation. Nervous influences or the development of compensatory collateral circulation may be responsible for such changes in symptoms. The difficulties in evaluation and the many factors that influence the pain of angina pectoris have been well described by Evans and Hoyle[6], and Gold[7]. We have attempted to circumvent some of these factors by using the "blind" method of testing in these studies[7] and by encouraging the patients not to change their mode of living in any way. The patients selected for this study, in most instances were suffering from relatively severe angina pectoris (*i.e.*, were having frequent attacks). It was decided that unless they were having many attacks, an attempt to evaluate any form of treatment was too difficult. The duration of the study has not been sufficiently long in all cases to exclude completely the possibility of natural remissions. In order to minimize the role of seasonal variations in the symptomatology, most of the patients were studied as the cold weather approached or was continuing. This is of some importance because with warm weather many cases of angina improve spontaneously.

The continuous course of khellin therapy was always of sufficient duration to permit the maximum effect that might be expected since optimum response is always anticipated after 2 weeks of therapy[10]. Placebo therapy was of sufficient duration to exclude even the prolonged effect of khellin. This point was exemplified by the fact that most of the patients who obtained beneficial results who were then changed to placebos usually noted the return of anginal attacks or an increase in the severity of attacks in 2 to 4 days after discontinuing khellin.

The greatest problems that khellin presented were the untoward side effects. The number and severity of these observed in this study diverges widely from those reported by others. Anrep *et al.*[2] in their series of 250 cases reported only mild, infrequent side effects after oral administration, namely, mild dyspeptic symptoms and insomnia in a few patients. In this series, the disturbing side effects occurred in over 50% of the cases. There was no uniformity as to the time of appearance of the untoward reactions. For the most part they had their onset during the first week of treatment. In a few patients they disappeared if the

drug was continued at the same dosage. Usually smaller doses of khellin eliminated the symptoms or reduced their severity so that the patient would continue treatment. A few, however, were unable to tolerate the medication.

There is a definite need for a long acting coronary vasodilator, as those that are available today are of dubious value. Khellin might meet this need, in an appreciable number of patients, if the untoward side effects could be controlled. Since the drug has a cumulative effect, an initial dose may be given to obtain an effective blood level and the patient then maintained on a lower daily dose. This is analogous to the method employed in digitalization. If further study bears this out, the usefulness of khellin will be enhanced and it may prove to be an effective aid in controlling the number and severity of anginal episodes in some patients.

Conclusions. 1. Khellin was administered to 53 ambulatory patients with angina pectoris. The dose employed was generally 40 mg. 3 times daily by mouth. The patients were permitted to carry on their activities unchanged during the period of study. Placebos identical in appearance were employed during periods of time as controls in such a way that neither patient nor observer was aware of the change in medication.

2. About 60% of the cases showed improvement, *i.e.*, used fewer nitroglycerin tablets, had fewer and milder attacks of pain and could walk greater distances.

3. There were uncomfortable side effects, namely, nausea, anorexia and dizziness in about 60% of the patients. These were a real deterrent to the use of the drug in many instances.

4. We believe that khellin has a definite value in the treatment of angina pectoris but that its usefulness will be enhanced if the undesirable side effects can be eliminated.

REFERENCES

1. **Anrep, G. V., Barsoum, G. S., Kenawy, M. R.,** and **Misrahy, G.**: Brit. Heart J., **8**, 171, 1946.
2. **Anrep, G. V., Kenawy, M. R.,** and **Barsoum, G. S.**: Am. Heart J., **37**, 531, 1949.
3. **Anrep, G. V., Kenawy, M. R., Barsoum, G. S.,** and **Fahmy, A.**: Gaz. Fac. Med. Cairo, **14**, 1, 1947.
4. **Ayad, H.**: Lancet, **1**, 305, 1948.
5. **Barsoum, G. S., Kenawy, M. R.,** and **El-Sheehy, A.**: J. Roy. Egyptian Med. Assn., **30**, 312, 1947.
6. **Evans, W.,** and **Hoyle, C.**: Quart. J. Med., **2**, 311, 1933.
7. **Gold, H., Kwit, N. T.,** and **Otto, H.**: J. Am. Med. Assn., **108**, 2137, 1937.
8. **Kenawy, M. R.,** and **Barsoum, G. S.**: Gaz. Fac. Med. Cairo, **13**, 39, 1945.
9. **Master, A. M., Nuzie, S., Brown, R. C.,** and **Parker, R. C., Jr.**: Am. J. Med. Sci., **207**, 435, 1944.
10. **Samaan, K.**: Quart. J. Pharm. and Pharmacol., **5**, 6, 1932.

HYPERTROPHY OF THE BRANCHES OF THE PULMONARY ARTERY, AND ITS POSSIBLE RELATIONSHIP WITH THE SO-CALLED PRIMARY PULMONARY ARTERIOSCLEROSIS IN 2 INFANTS WITH HYPERTROPHY OF THE RIGHT HEART

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This study was made with the aim of explaining a hypertrophied right heart found during an autopsy of a female infant. Histological examination of branches of the pulmonary artery revealed some important changes, which might explain the reason for the cardiac hypertrophy. It is believed that the pathological changes might also throw some light on the problem of the so-called primary pulmonary sclerosis. The study is based on 2 cases. Stimulated by the first (Case 1) to study the problem of congenital right heart hypertrophy, I found a similar case in the archives of this Institute (Case 2), which has also been included.

Clinical and Pathological Reports: Case 1*. A girl with cleft palate, born at term to nonsyphilitic parents; weight at birth 3 kg. No other congenital abnormalities were found. Soon after birth marked cyanosis was noted. The cyanosis appeared in attacks accompanied by hyperpnea or dyspnea. During her first days feeding was difficult because of the cleft palate. Sulphadiazine 0.2 to 0.4 gm. per day was given to the infant as preventive against pulmonary infection. She did not develop or gain in weight and the attacks of cyanosis became more and more frequent, until she became permanently cyanotic. Roentgen-ray examination of the chest did not reveal any abnormalities. When 6 weeks old she developed febrile bronchopneumonia and died in 6 days. The physicians in charge suspected that the cyanosis was due to a malformation of the bronchial tree which did not allow a normal gaseous exchange.

Autopsy: The pertinent autopsy findings were as follows: palatoschisis; foci of beginning purulent bronchopneumonia, not recognizable as such on macroscopical examination of lungs. Heart weighed 45 gm. (average normal at this age, 25 gm.); the apex consisted of right ventricle only, which was markedly hypertrophied and dilated. Papillary muscles were thick and somewhat flattened. The ductus arteriosus was closed. The foramen ovale was found covered by a thin transparent membrane, not completely adherent to the septum. Left ventricle normal. Microscopical examination of heart did not show increased amount of glycogen or lipids. Muscle fibres of right ventricle, although not measured, did not seem enlarged or thickened. Nuclei seemed normal.

Macroscopical examination of other organs failed to reveal other gross abnormalities.

Histological examination of the lungs revealed the presence of a few scattered areas of beginning purulent bronchopneumonia. Besides, changes were noted in the pulmonary arteries. All arteries examined showed thickening of their walls, due to increase in thickness of all tunics. Elastic fibers were very numerous in all vessels and were present also in small arteries, which do not usually contain elastic tissue. The changes observed in the arteries were quantitative rather than qualitative. The elastic membranes, the muscular layer and the collagenous fibers, were all of approximately "normal" appearance, but they were overdeveloped as compared with normal arteries of equal diameter. The increase in elastic tissue was apparent also in the veins and in the alveolar walls. No atheromatous changes were discovered anywhere except

* The author is indebted to Dr. Berman and Dr. Roth of the Pediatric B Department of this Hospital for the clinical information.

for the stem of the pulmonary artery. Vessels of the systemic circulation appeared perfectly normal.

The case may be summarized as follows: An infant having attacks of cyanosis from birth developed bronchopneumonia at the age of 6 weeks. The pathological substrate of these attacks seems to be found in the pulmonary arterial tree in the form of a hypertrophic process believed to be congenital.

Case 2†. A girl born at term to apparently healthy parents. Clinically, there was pallor and a very marked cyanosis, which temporarily responded to oxygen treatment. The infant died on the day after its birth.

The pertinent autopsy findings (Dr. H. Ungar, of this Institute) were: Body weight 5 kg; length 55 cm. Heart weighed 44 gm., (average normal, 19 gm.) Marked dilatation and hypertrophy of right atrium and ventricle. Purulent bronchopneumonic foci were found in the bases of both lungs.

Histologic examination of the lungs revealed appearances similar to those of Case 1. In the heart, as in Case 1, no cause could be found for the hypertrophy of the right side, that is, no increase in glycogen or fat content of myocardium.

Statistical Verification of the Presence of the Hypertrophic Process. Studies appearing in literature are often based mainly on impressions. It is often difficult to differentiate between facts and impressions which develop upon preconceived ideas, or even upon differences in technique. It was therefore thought necessary to employ accurate statistical methods in this study.

Collection of Data: Case 1 and Case 2 were considered separately. An unselected series of 7 other consecutive autopsies of infants less than 3 months old (performed after the autopsy on Case 1) served as controls.

From the lungs of all 9 cases, fixed and preserved in 4% formaldehyde, blocks were made and embedded in paraffin. From each lung blocks were cut from two analogous sites: the hilum area and the antero-inferior margin of the lower lobe. Sections were cut at 10μ thickness and complete series were stained simultaneously. All measurements were made on sections stained with Weigert's elastic combined with Van Gieson's stain.

Vessels were measured with an ocular micrometer, previously gauged with a Zeiss objective micrometer. In order to lessen the chances of mistaking bronchial vessels for pulmonary ones, no vessel lying near a bronchus was included. Veins, whenever recognized as such, were also left out.

In each section of the control group, 25 arteries were examined; 50 arteries were examined in each of the sections of the 2 cases. Thus 100 arteries were examined for each of the 2 cases. The total number of arteries examined in the control group was 350.

The statistical data for the control group were pooled in order to obtain a more accurate picture of "normalcy". It should be noted, too, that there were no significant differences among the values obtained in the individuals of this group, and that the group could therefore be taken to be homogeneous.

The following data were compared in each of the 2 cases with the controls, comparing arteries of equal external diameter: 1, Width of arterial wall, in toto; 2, Width of media; 3, Width of adventitia; 4, Character of the arterial wall outside the endothelium, whether homogeneous, or composed of distinct tunics; 5, Presence and distribution of elastic tissue.

Statistical Elaboration of Data.* 1.*Width of the Arterial Wall.* The average width of the arterial walls is larger in both cases as compared with that of controls (Chart 1). The difference is more marked in Case 1. Not all the data could be examined as to their statistical significance as the numbers were not always sufficient. Table 1 shows that significance exists in the group of external diameter between 20 to 29μ and 50 to 59μ. On the other hand, as the averages of both cases

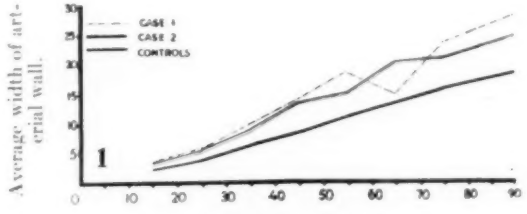
† The clinical and pathological data of this case are not complete as information about the case, which occurred a few years before this study was begun, was obtained from hospital records.

* The Author is grateful to Dr. U. Foa of this Institute for the statistical elaboration of the data.

were always higher than those of the controls, it is permissible to consider the observations made on vessels of various diameters in terms of composite probability, and therefore to conclude that the differences were significant along the whole line.

It should also be noted that the standard error of the difference between means has been calculated with the aid of the so-called short-formula, which presupposes a lack of correlation between the series considered. Since it is obvious that such correlation does exist, the values of the Critical Ratio are in reality higher than those reported.

2. *Width of the Different Arterial Coats.* The intima was not considered in the statistical part of the study for the following reasons: (a) because of its rather small width the error of measurement would be relatively large; (b) in many arteries it was not recognizable; (c) the great variability in its width, within the same section, especially in the arteries of the smallest caliber (30μ and below).



External diameter of vessels.

TABLE 1.

A. Width of the Arterial Wall.

External diameter of vessels in μ	*Case 1:*		*Case 2.*		*Controls*	
	No. of vessels	*average width*	*No. of vessels*	*average width*	*No. of vessels*	*average width*
10–19	7	3.57	5	3.40	25	2.84
20–29	22	5.68	27	5.55	78	4.35
30–39	28	9.75	26	9.07	88	6.79
40–49	17	13.94	15	13.53	55	8.92
50–59	11	18.54	8	15.00	41	11.24
60–69	1	15.00	4	20.00	16	13.50
70–79	5	23.60	5	20.80	12	16.08
80–99	3	28.00	2	24.50	10	18.60
100+	6	62.00	5	37.40	25	37.36

B. Comparison Between the 2 Cases and the Controls.

External diameter of vessels, in μ	*Case 1 v. Controls Critical Ratio*	*Case 2 v. Controls Critical Ratio*
20–29	3.72	2.83
30–39	6.08	3.83
40–49	5.34	5.59
50–59	8.26	2.38

It has been noted, especially in Case 1, that the intima of many small arteries was thickened, often rather irregularly, so that its width varied at different points of the same perimeter.

Charts 2 and 3 and Tables 2 and 3 show that both the adventitia and the media were thicker in the 2 cases than in the controls. Although some of the Critical Ratio values were not signi-

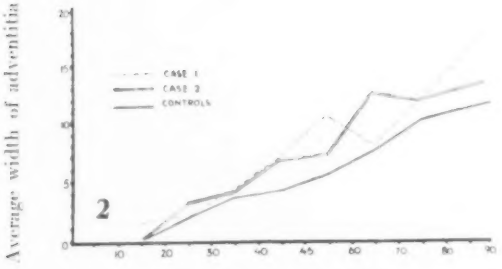


TABLE 2.—WIDTH OF MEDIA AND ADVENTITIA.

External diameter of vessels in μ	*Case 1.*			*Case 2.*		
	No. of vessels*	*average value*		*No. of* vessels*	*average value*	
		Media	*Adventitia*		*Media*	*Adventitia*
10–19	2	3.00	1.50	1	3.00	0.00
20–29	13	3.07	2.07	13	3.38	2.92
30–39	28	3.78	4.35	25	3.80	3.92
40–49	17	4.88	7.17	15	5.13	6.66
50–59	11	6.00	10.72	8	6.00	7.12
60–69	1	5.00	8.00	4	5.75	12.25
70–79	5	10.00	12.00	5	6.80	12.00
80–99	3	7.66	17.66	2	9.00	13.50
100+	6	23.83	36.33	5	14.40	21.40

External diameter of vessels in μ	*Controls*		
	No. of vessels	*average value*	
		Media	*Adventitia*
10–19	0		
20–29	13	3.00	2.07
30–39	48	3.33	3.81
40–49	45	3.77	4.15
50–59	39	4.33	5.74
60–69	16	4.50	7.56
70–79	12	4.75	10.25
80–99	10	5.60	11.60
100+	25	8.76	26.60

* In the smallest diameter groups the number of vessels represents only those arteries in which the walls were differentiated, and a media and adventitia were distinguishable.

ficant in themselves, it may be assumed, for the reasons already stated, that the differences in both these coats between each of the 2 cases and the controls were not due to chance.

3. *Differentiation of the Arterial Walls.* Normally no distinction can be made between arterial coats in the smallest pulmonary arteries (below 20μ in diameter). There is no visible subendothelial layer, and the endothelium rests on a fibromuscular mantle. In somewhat larger arteries, which still do not contain stainable elastic fibres, the media can be easily distinguished from a collagenous adventitia. Arteries were therefore divided in this study into 2 groups: those with a differentiated wall, and those lacking such a differentiation.

The percentage of arteries with a differentiated wall (per 100 arteries of each size) is given in Chart 4. It can be seen that the process of differenti-

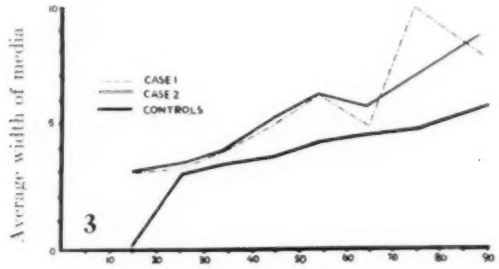


TABLE 3.—COMPARISON BETWEEN THE 2 CASES AND THE CONTROLS IN THE WIDTH OF MEDIA AND ADVENTITIA.

External Diameter of vessels in μ	*Case 1 v. Controls Critical Ratio*		*Case 2 v. Controls Critical Ratio*	
	Media	*Adventitia*	*Media*	*Adventitia*
20–29	0.19	0.00	1.27	1.89
30–39	1.69	1.12	2.12	0.23
40–49	2.48	4.36	3.09	4.36
50–59	4.54	6.18	3.61	1.15

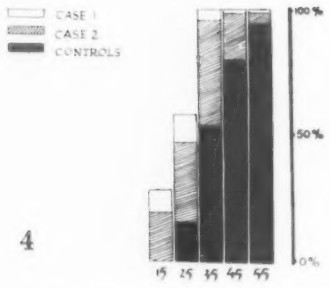
TABLE 4.—DISTRIBUTION OF ELASTIC TISSUE.

Case	*Elastica*	*External diameter of vessels (in μ)* 20–29** C_c*	30–39 C_c*	40–49 C_c*	50–59† C_c*
1	Absent	63.64	25.02	0.00	9.10
	Suspected	9.09	17.85	17.66	0.00
	External layer only	18.18	46.42	41.17	36.36
	Both layers present	9.09	10.71	41.17	54.54
	TOTAL	100.00	100.00	100.00	100.00
2	Absent	59.28	34.62	13.33	0.00
	Suspected	14.81	19.23	13.33	0.00
	External only	18.51	38.46	60.01	62.50
	Both present	7.40	7.69	13.33	37.50
	TOTAL	100.00	100.00	100.00	100.00
Controls	Absent	93.60	76.15	43.65	41.48
	Suspected	2.56	7.95	10.90	2.43
	External only	3.84	14.77	29.09	39.02
	Both present	0.00	1.13	16.36	17.07
	TOTAL	100.00	100.00	100.00	100.00

* The number of vessels from which the percentages have been derived can be noted in Table 1.
** In vessels less than 20 μ in diameter, no elastic tissue is recognizable.
† In vessels more than 60 μ in diameter, elastic tissue is almost always present with at least 2 layers.

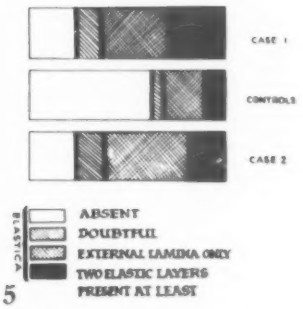
ation has pushed into much smaller arteries in each of the 2 cases than in the controls. The significance of these differences has been calculated by using the χ^2 method. The distribution of the series in Case 1 compared to the control yielded a χ^2 value of 39.10. Case 2 yielded a χ^2 value of 25.91. Both values are highly significant and correspond to a probability larger than 99% that the samples compared were not taken from the same universe, that is, that each of the 2 cases differs significantly from the controls[18].

4. *Elastic Tissue.* As stated above, all sections were stained simultaneously in the same staining solutions, so that a comparison between the amount



4

Percentage of vessels with walls composed of 3 tunics.



5

Elastic tissue (in vessels of diameter from 20 to 60 microns).

TABLE 5.—PROBABILITY THAT THE DIFFERENT DISTRIBUTION OF THE ELASTIC TISSUE IN THE 2 CASES AND THE CONTROLS IS NOT DUE TO CHANCE.

External diameter of vessels in μ	*Case 1 v. Controls* %	*Case 2 v. Controls* %
20–29	99	99
30–39	99	99
40–49	99	90
50–59	95	80

of elastic tissue is permissible. In order to permit a statistical evaluation, vessels were divided into 4 categories: 1, Arteries in which no elastic fibres were discerned; 2, Those in which the presence of such fibres was suspected, but not clearly seen (as only faintly staining delicate fibrils were observed); 3, Arteries with a definite elastic layer, situated on the outer perimeter of the media; 4, Arteries with 2 definite elastic layers, with or without additional elastic fibres.

Chart 5 and Tables 4 and 5 show that in each of the 2 cases elastic tissue was found to be more widespread than in the controls and was present also in very small arteries, which normally do not contain an elastic layer. The diagram is also based on a calculated percentage in 100 arteries of various sizes.

Table 4 and 5, which has been worked out on a χ^2 calculation[37], prove that the differences in the amount of elastic tissue between each of the 2 cases and the controls, is statistically significant.

Discussion of the Statistical Findings. The statistical examination of the data seems to prove beyond reasonable doubt that the pulmonary arteries of the 2 cases and especially those of the first, deviate significantly and markedly from the normal. This deviation is expressed by thickening of all the arterial coats; presence of a neat differentiation of arterial coats in the walls of small arteries; increased amount of elastic tissue.

The deviation is probably greater in reality than the calculated values for the reasons already stated as well as because: Arteries were divided into groups according to their external diameter. It is obvious that a thickening of the wall of any artery might bring it into a larger diameter group, in which case it would be compared with larger arteries of the control group.

It is well known that there are numerous pitfalls in studies based on observations such as those described above. Rigor mortis or faulty fixation might also produce appearances similar to those of arterial hypertrophy by producing tortuosity and apparent

thickening of elastic and other layers. It is believed, however, that the changes described in this paper are real for the following reasons:

1. Evelyn[17] reports that measurements of the width of arterial tunics made by different authors using different techniques have yielded similar results.

2. In both cases described in this paper, there were other changes concomitant with the arterial hypertrophy which could not be due to the above mentioned pitfalls: 1, Presence of elastic fibres in vessels which do not contain them normally; 2, Differentiation of the walls of small arteries which normally are not differentiated.

Discussion. A. PATHOLOGICAL FINDINGS. The 2 cases have many similar points: 1. Cyanosis was present in both. There were attacks of cyanosis in the first case, while in the second the clinical chart does not specify whether the cyanosis was continuous or not. The condition can perhaps be explained by the pathological findings in the arteries: It might be assumed that arterial hypertrophy would make the arteries more rigid and cause local arterial hypertension. Thus Gross *et al.*[22], who studied sclerotic changes in the coronary arteries, stated: "That such fibro-elastic transformation of these vessels renders them more or less passive, i.e., less susceptible to vasomotor control seems evident. . . . the fibro-elastified vessels probably cannot undergo sufficient vasodilatory changes to compensate for the narrowing". On the other hand, proof has been given by Euler and Liljenstrand[16], and by Logaras[32], that such a vasomotor control is normally operating in the pulmonary circulation.

2. In both cases the right heart was hypertrophied. This finding is regularly encountered in cases of pulmonary arteriosclerosis to which these cases may perhaps be compared.

The relationship between right heart hypertrophy and pulmonary sclerosis has been regarded by most authors as a relation of cause and effect. Torhorst (cited by Schuette[43]) proved that increased pressure in the lesser circulation provokes sclerotic changes in the larger arterial branches only. It is therefore considered reasonable to assume that the congenital hypertrophic changes might be the cause of the so-called "idiopathic hypertrophy of the right heart".

The hypertrophic condition of the right side of the heart is not thought to be due to a congenital malformation contemporaneous to the changes in the pulmonary arteries, because of the following reasons: a, The hypertrophic process affected the right heart only; b, The changes in the pulmonary arteries are thought to be a sufficient reason for the cardiac hypertrophy.

Kugel and Stoloff[29] have expressed the hope that the term "congenital idiopathic hypertrophy of the heart" might disappear from the literature as knowledge of heart diseases in infancy increases. It is suggested that this study may be of some help in eliminating one group of cases included under this term.

3. In both cases death was due to bronchopneumonia. The insufficient blood supply caused by the arterial hypertrophy probably may be regarded as a strongly coadjuvating factor.

It should also be mentioned that the changes in the pulmonary vessels are taken to be primary and not secondary to the bronchopneumonia, that is, it is believed that the hypertrophic changes were present at birth. The reasons for this belief are: 1. The attacks of cyanosis antedated the bronchopneumonia and were apparent soon after birth;

2. Acute suppurative bronchopneumonia which lasts a few days is known to destroy collagenous and elastic tissue and not to produce their proliferation.

The pathological changes described above are entirely hyperplastic, and except in the main stems of pulmonary artery no degenerative changes were observed. Whether they should be included in the complex term of arteriosclerosis or not depends on the exact meaning and definition of that term. Most authors (Aschoff[2], and Haas[25]) make a clear distinction between the sclerotic process of ageing and arteriosclerosis in a narrower sense which affects persons of all ages. The nature of the arteriosclerotic process in the narrower sense is regarded by some authors as the result of a primary lipoid infiltration of the arterial walls (Anitschkow[1], Aschoff[2], and Leary[30]). Some (Thoma, Torhorst, Hueck, and others, cited by Vanzetti[47]) believe that the primary lesion of arteriosclerosis is a connective proliferation.

Following the views of the second group the changes described in the pulmonary arteries should be regarded as early sclerotic or presclerotic. It is believed that upon such changes, clear arteriosclerotic lesions might develop in due course.

The study of pulmonary arteriosclerosis began almost 100 years ago. Dittrich[11] appears to have been the first to describe this condition; Posselt[38,39] first correlated the pathological findings with a definite clinical picture.

Various conditions, representing very different pathological entities, but giving similar clinical symptoms, have been described under this heading. This confusion caused some authors (Norris[36]) to regard pulmonary sclerosis as a syndrome and not as a disease entity. It is thought necessary therefore to draw a sharp line of demarcation between sclerosis of the pulmonary artery and inflammatory conditions of the same, such as: syphilitic pulmonary arteritis; inflammatory pulmonary arteritis (Rothschild and Goldbloom's case[41]; and Schuette's[43]); or the pulmonary involvement in thromboangiitis obliterans (Hausner and Allen[26]).

The subject of pulmonary sclerosis has been summarized by Posselt[38,39], Ljungdahl[31], and, more recently, by Brenner[4]. The disease is usually secondary and as such is most often associated with conditions which are supposed to increase blood pressure in the lesser circulation. The various conditions in which secondary sclerosis occurs, as well as plausible interpretation of its pathogenesis, can be found in Moschcowitz's[35] or Brenner's[4] papers. It should be noted that according to most authorities secondary sclerosis affects mainly the large and medium sized branches of the pulmonary artery, is associated with conditions believed to increase pulmonary blood pressure, and is usually of the atheromatous type. The disease is also invariably associated with right ventricular hypertrophy (Brenner[4]).

The relationship between pulmonary sclerosis (secondary) and pulmonary hypertension is accepted by most workers: Bryant[6], Sanders[42], Hart[24], Moschcowitz[35]; while others (De Navasquez *et al.*[10], Brenner[4]) do not regard this relationship as proved. Experimental studies show that increased intra-alveolar pressure produces in rats degenerative lesions in the arterioles (Smith *et al.*[45]); but on the other hand Karsner *et al.*[28] failed to obtain marked changes in lung arterioles adopting a procedure which, in the authors' belief, might cause an increased pulmonary arterial pressure. The disease is invariably associated with right ventricular hypertrophy (Brenner[4]). Pri-

mary sclerosis differs from the secondary one in that it affects mainly the smallest arteries (see for example Roessle[40]). Eppinger and Wagner[15], and later Kaump and Dry[27] pointed out that the cause and effect relationship between arteriosclerosis and hypertensive symptoms in the lesser circulation should be viewed in the same way as in the major circulation. According to them hypertensive symptoms will occur only when the sclerotic process affects the smallest arteries. Arteriosclerosis of the larger vessels, however severe, does not cause hypertension. In the same way as in the renal arterioles, arteriolar sclerosis in the lesser circulation is invariably associated with hypertension.

Hart[24] divided his cases of primary pulmonary sclerosis into 2 groups. In the first were included elderly men in whom, in spite of the fact that no cause for the sclerosis was revealed at autopsy, there was reason to believe that during their life span they might have been exposed to various factors which determined this condition. The second group included young men in whom no such cause could be involved. Hart assumed therefore that the condition is determined by a congenital abnormality of the pulmonary arterial tree. This opinion, first voiced by Moenckeberg[34] was accepted by many authors, like Ljungdahl[31], Foltz[19], Gilmour and Evans[20], and Gold[21]. Further evidence in favor of the presence of a congenital factor in pulmonary sclerosis is given by a number of cases in which symptoms dated from birth or during the first few months of life, and autopsy was performed early in infancy (Durante[13], Bryant and White[7], Darley and Doan[9], Cross and Kobayashi[8]).

The fact that a congenital factor can be operating in arteriosclerosis in other locations has been proved by a number of observations on coronary sclerosis in infancy (Brown and Richter[5], Scott and Miller[14], Stryker[46]). Dock[12] reported hypertrophic changes in the coronaries of infants which in his opinion have a bearing on the subsequent development of coronary sclerosis. Dock's study, confirmed by Minkowski[33], points to a definite relationship between congenital hypertrophic changes in the arteries and arteriosclerosis. It is believed that a similar relationship exists between the hypertrophic changes in the pulmonary arteries described in this paper and a fully developed pulmonary arteriosclerosis.

The changes observed in the pulmonary arteries of the 2 cases may be regarded as sclerotic changes of grade I, according to the grading method used by Kaump and Dry[27]. It is possible that these quantitative changes passed unobserved by a number of investigators, who looked for degenerative processes in the arterial walls in order to explain the "pulmonary hypertension syndrome" (De Navasquez *et al.*[10], East[14]). The lack of degenerative changes in the arteries is not surprising, as in a number of cases of pulmonary arteriosclerosis no such changes were found (Moenckeberg[34], Sanders[42], Foltz[19]).

Various opinions were expressed on the pathogenesis of primary pulmonary sclerosis. Thus, Bredt[3] regards it as a result of an unknown toxin. Rothschild and Goldbloom[41] believe their case was due to allergic phenomena. Recently Harrison[23] put forward experimental evidence suggesting that primary pulmonary arteriosclerosis might be due to the organization of multiple thrombi or emboli. It is believed that the present study brings evidence to support the views of previous workers who took primary pulmonary sclerosis to be a result of congenital factors.

Summary and Conclusions. 1. Two cases of so-called congenital "idiopathic" hypertrophy of the right heart are described.

2. In both cases hypertrophic changes of the pulmonary arteries, expressed in thickening of all arterial coats, increased amount of elastic tissue, and presence of a neat differentiation of coats in the arterial wall of the smallest arteries, were observed.

3. A statistical examination of these findings, compared with the findings in 7 control cases, proved that the difference is statistically significant.

4. The opinion is expressed that the findings reported might constitute the anatomical background or the first step toward primary pulmonary sclerosis, which is believed to be due, at least in some cases, to the described congenital malformation.

5. It is further thought that congenital hypertrophy of the small pulmonary arteries might be the cause of the right heart hypertrophy.

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REFERENCES

1. **Anitschkow, N.**: Beitr. z. path. Anat. u.z. allg. Path., **56**, 379, 1913 (cited in Cowdry's Arteriosclerosis, New York, Macmillan, 1933).
2. **Aschoff, L.**: In Introduction, Cowdry's Arteriosclerosis, New York, Macmillan, 1933.
3. **Bredt, H.**: Virchows Arch., **284**, 126, 1932.
4. **Brenner, O.**: Arch. Int. Med., **56**, 211, 457, 724, 976 and 1198, 1935.
5. **Brown, C. E.**, and **Richter, J. M.**: Arch. Path., **31**, 449, 1941.
6. **Bryant, J. H.**: Guy's Hosp. Rep., **55**, 83, 1901.
7. **Bryant, J. H.**, and **White, W. H.**: Ibid., **55**, 17, 1901.
8. **Cross, K. R.**, and **Kobayashi, C. K.**: Am. J. Clin. Path., **17**, 155, 1947.
9. **Darley, W.**, and **Doan, C. A.**: Am. J. Med. Sci., **191**, 633, 1936.
10. **De Navasquez, S.**, **Forbes, J. R.**, and **Holling, H. E.**: Brit. Heart J. **2**, 117, 1940.
11. **Dittrich, E.**: Programm zum Eintritt in die med. Fakultaet der Friedrich Alex. Univ. zu Erlangen, 1850 (Cited by Ljungdahl, 1915).
12. **Dock, W.**: J. Am. Med. Assn., **131**, 875, 1946.
13. **Durante:** Bull. Soc. Anat. de Paris, **6**, 97, 1899 (cited by **Ballantyne, J. W.**: Manual of Antenatal Pathology and Hygiene, Edinburgh, Green, 1902).
14. **East, T.**: Brit. Heart J., **2**, 189, 1940.
15. **Eppinger, H.**, and **Wagner, R.**: Wien. Arch. f. Int. Med., **1**, 83, 1920.
16. **Euler, U. S. V.**, and **Liljenstrand, G.**: Acta Physiol. Scand., **12**, 301, 1946 (cited by **Logaras**).
17. **Evelyn, K. A.**: Am. J. Med. Sci., **214**, 312, 1947.
18. **Fisher, R. A.**: Statistical Methods for Research Workers, London, Oliver & Boyd, 1936.
19. **Foltz, P.**: Policlin. (Sez Med.), **40**, 539, 1933.
20. **Gilmour, J. R.**, and **Evans, W.**: J. Path. and Bact., **58**, 687, 1946.
21. **Gold, M. M. A.**: Arch. Int. Med., **78**, 197, 1946.
22. **Gross, L.**, **Epstein, E. Z.**, and **Kugel, M. A.**: Am. J. Path., **10**, 253, 1934.
23. **Harrison, C. V.**: J. Path. and Bact., **60**, 289, 1948
24. **Hart, C.**: Berl. klin. Woch., **33**, 1243, 1916.
25. **Haas, G. M.**: Arch. Path., **27**, 334, 1939.
26. **Hausner, E.**, and **Allen, E. V.**: Proc. Mayo Clin., **15**, 7, 1940.
27. **Kaump, D. H.**, and **Dry, T. J.**: Arch. Int. Med., **61**, 1, 1938.
28. **Karsner, H. T.**, **Simon, M. A.**, and **Fujinawa, T. F.**: Arch. Path., **31**, 584, 1941.
29. **Kugel, M. A.**, and **Stoloff, E. G.**: Am. J. Dis. Child., **45**, 828, 1933 (cited by **Weisman, S. J.**: Arch. Path., **33**, 365, 1942).
30. **Leary, T.**: Arch. Path., **32**, 507, 1941.
31. **Ljungdahl, M.**: Untersuchungen ueber die Arteriosklerose des Kleinen Kreislauf, Wiesbaden, Bergmann, 1915.
32. **Logaras, B.**: Acta Physiol. Scand., **14**, 120, 1947.

33. **Minkowski, W. L.:** Am. J. Med. Sci., **214,** 623, 1947.
34. **Moenckeberg, J. G.:** Deut. med. Woch., **33,** 1234, 1907.
35. **Moschcowitz, E.:** Am. J. Med. Sci., **174,** 388, 1927.
36. **Norris, R. F.:** Bull. Johns Hop. Hosp., **59,** 143, 1936.
37. **Pearl, R.:** Introduction to Medical Biometry and Statistics, 3d ed., Philadelphia, W. B. Saunders, 1940.
38. **Posselt, A.:** Volkmann's Samml. klin. Vortr., Leipzig, Breitkopf, 1908, n. F. 504-507. (Inn. Med., 149).
39. Idem: Erg. d. allg. Path. u. path. Anat., **13,** 298, 1909 (edited by Lubarsch, D., and Ostertag, R.).
40. **Roessle, R.:** Muench. med. Woch., **55,** 377, 1908.
41. **Rothschild, M. A.,** and **Goldbloom, A. A.:** Arch. Int. Med., **61,** 600, 1938.
42. **Sanders, W. E.:** Ibid., **3,** 257, 1909.
43. **Schuette, H.:** Centralb. f. allg. Path. u. path. Anat., **25,** 483, 1914.
44. **Scott, E. P.,** and **Miller, A. J.:** J. Ped., **28,** 478, 1946.
45. **Smith, F. J. C., Bennet, G. A.,** and **Heim, J. W.:** J. Exp. Med., **56,** 79, 1932.
46. **Stryker, W. A.:** Am. J. Dis. Child., **71,** 280, 1946.
47. **Vanzetti, F.:** l'Arteriosclerosi, Torino, Bibl. Cult. Med., 1928.

ACUTE PRIMARY PERICARDITIS

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Acute pericardial involvement secondary to, or associated with, certain specific diseases is well known, adequately described in the literature, and almost always sought for by the examining physician. Many physicians however are unaware of the existence of a primary inflammatory disease of the pericardium, the etiology of which is unknown, and which we feel is best classified under the heading of acute primary pericarditis of unknown origin. The diagnosis of this condition is probably more often missed than made. When the course is mild, and the laboratory examinations inadequate, the illness may be passed off as a cold, grippe or pleurisy. When the symptoms are severe, and the pain intense and unusual in distribution, the differential diagnosis from coronary occlusion and the acute surgical abdomen may be difficult to make.

The general medical literature has not given adequate emphasis to this condition. In 1934 Willius[15] described a case which followed acute pharyngitis and stated that "it is fairly common to find acute serofibrinous pericarditis with effusion and we are frequently amazed at the recovery which these patients make!" Barnes and Burchell[1] described this illness under the heading of acute benign nonsuppurative pericarditis, stressing the characteristics which differentiated it from coronary occlusion. Wolff[16], presenting his cases of idiopathic pericarditis, and Coffen[5], in his case report, also point out that this disease may simulate myocardial infarction. Logue and Wendkoss[9] state that 6 of their 17 cases of acute pericarditis of the benign type were mistakenly diagnosed as coronary occlusion on admission. Nathan and Dathe[10] observed pericarditis with effusion after upper respiratory tract infections in 8 patients in whom no intrathoracic disease was found. The association of this disease with atypical pneumonia was described by Finkelstein and Kleiner[6] and Smalley and Ruddock[11]. Burchell[3], in his excellent review of the subject, presents a large group of illustrative cases, discussing in detail the symptoms, signs and differential diagnostic features under the heading of acute nonspecific pericarditis. Bellet and McMillan[2], Vander-Veer and Wagner[13], and others, who have thoroughly discussed the general subject of acute pericarditis, make only casual mention of cases of unknown etiology. White[14], Levine[8], Cecil[4], and other textbooks of cardiology and medicine give little or no consideration to this condition.

The impression gained from the lit-

erature is that the condition is entirely benign, but this may not necessarily be true. It has a tendency to recur: 2 of our cases had at least 2 proven recurrences. Such recurrences may conceivably give rise to serious sequelae. Harrington[7] surgically treated 24 patients with constrictive pericarditis. In 8 of these cases, although no definite etiologic factor was found, a history of 1 or more previous attacks of some pulmonary infection such as pneumonia or influenza was obtained. As will be seen from our case reports, such pulmonary infections occur in association with acute primary pericarditis. Sprague and White[12] also are of the belief that adhesive pericardial fibrosis is caused by an infection of unknown etiology.

We believe that until a specific etiologic factor is discovered the best descriptive name of the disease is acute primary pericarditis. It is our purpose to reëmphasize the clinical features of the condition and include our experience with 5 additional cases.

Case Reports. CASE 1. (No. 184144) R.L., a 30 year old married white female housewife, was admitted to the surgical service of Beth El Hospital on May 6, 1948, complaining of severe upper abdominal pain and lower substernal pain. The history indicated that the first of a number of such attacks occurred 8 months prior to admission and recurrences took place at intervals of 1 or more months. On previous occasions the pain lasted a few days, was accompanied by fever and subsided spontaneously. The patient felt that at times these attacks were precipitated by fatty foods. Frequently she vomited during the attack. Her physician had told her she had gall bladder disease. Examination on admission disclosed a temperature of 101°, pulse 102, respirations 28 and blood pressure 120/80. There was moderate dyspnea. There was impaired resonance at both lung bases. There were marked tenderness and muscle spasm in the epigastrium and right upper quadrant. A tentative diagnosis of acute exacerbation of chronic cholecystitis and cholelithiasis complicated by bronchopneumonia was made. Medical consultation was requested because of the pneumonia. In addition to the above findings a pericardial friction rub and paradoxical pulse were also observed. Further questioning disclosed that the pain was aggravated by deep inspiration, swallowing, cough and motion of the trunk. Roentgenogram of the chest (Fig. 1) revealed enlargement of the cardiac silhouette consistent with a diagnosis of pericardial effusion, and signs of bronchopneumonia in both bases. The electrocardiogram (Fig. 2) was diagnostic of acute pericarditis. Codeine afforded some relief of pain. There was no dramatic response to 100,000 units of penicillin given intramuscularly every 3 hours. The temperature gradually subsided to become normal on the 6th day. At this time the pain was

FIG. 1 (CASE 1).—Pericardial effusion, bronchopneumonia May 7, 1948.

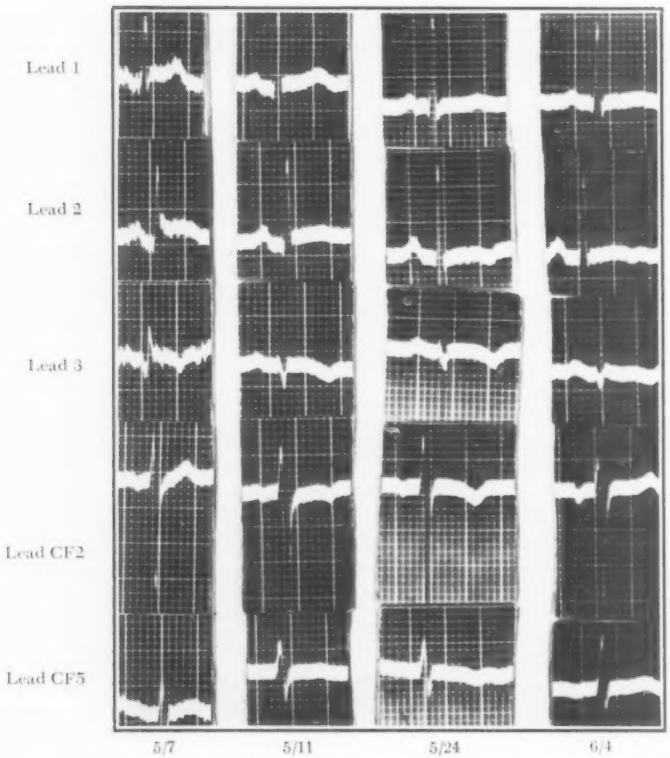

FIG. 2 (CASE 1).—Serial Electrocardiograms, May 7, 1948, to June 4, 1948.

FIG. 3 (CASE 1).—Normal chest Roentgenogram, June 5, 1948.

completely relieved. One week later, on the 13th day, there was a recurrence of dull substernal pain, the temperature rose to 102.6°, the pulse to 130, and a pericardial friction rub was again audible. A small pleural effusion collected at the left base. Thoracentesis yielded 350 cc. of a serous fluid. The temperature subsided spontaneously 3 days later and the pain disappeared. Repeated roentgenograms (Fig. 3), the first and last of which are shown, showed a gradual decrease in the size of the heart, complete resolution of the bronchopneumonia and absorption of the pleural effusion. Serial electrocardiograms (Fig. 2) showed the classical changes of acute pericarditis beginning with RS-T elevations in the standard leads, followed by flattening of T in lead 2 and CF5 and inversion of T in CF2, then flattening of T in lead 1 and inversion of T in all other leads. The elevated RS-T segments returned to the isoelectric level. Finally there was a return toward positivity of all the T waves. The electrocardiogram taken prior to discharge showed a reversion toward the normal pattern. The chest film was negative. The patient left the hospital well on June 4, 1948.

Laboratory Data. Many blood counts showed a hemoglobin which varied from 55 to 80%, red blood cells from 2,600,000 to 4,400,000, white blood cells from 16,000 to 8,000, polymorphonuclears from 80 to 63%. The sedimentation rate dropped from 43 mm. per hour on admission to 10 mm. per hour on May 27, and rose again to 24 mm. per hour on June 2. Urinalyses were negative. Agglutination tests against all the known organisms, including the cold agglutination test, were negative. Smears and cultures of many sputa and gastric washings were negative for tubercle bacilli. The Mantoux test was negative in a dilution of 1: 10,000. Many red blood cells, inflammatory cells and mesothelial cells were found in the pleural fluid. Smears of this fluid were negative, as were culture and guinea pig inoculation. Gall bladder and gastrointestinal roentgenologic series were negative.

Follow Up. One month after discharge the patient was readmitted to another hospital for a recurrent episode. The findings there were essentially those which we observed. She was discharged after 4 weeks. Since that time we have examined her twice at our follow-up clinic, the last time June 12, 1949. She has remained well. Physical examination, chest film and electrocardiogram are entirely normal.

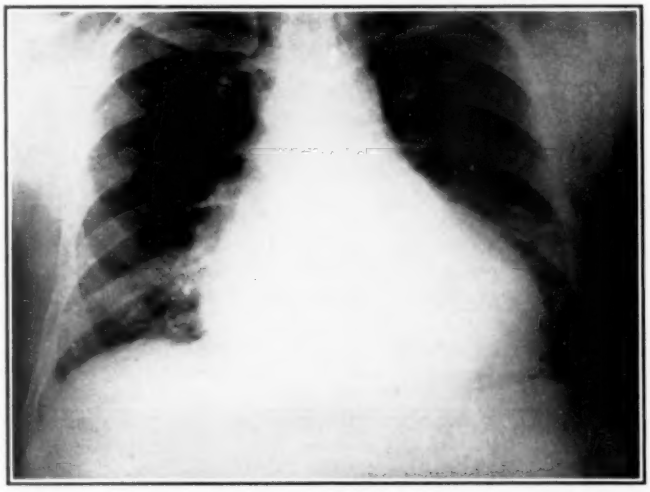

FIG. 4 (CASE 2).—Pericardial effusion, bronchopneumonia Oct. 19, 1948.

Comment. This case illustrates the recurrent nature of the attacks of acute pericarditis, the typical symptoms, signs, course, roentgenographic and electrocardiographic findings, the absence of an etiologic factor, the confusing abdominal symptoms, and the associated pulmonary lesions. Follow-

up for one year shows no serious sequelae.

CASE 2. (No. 189518) A.C., a 50 year old white male, was admitted to Beth El Hospital on Oct. 17, 1948, complaining of malaise and irregular fever of 1 week's duration. One month prior to admission the patient was ill with an upper respiratory infection and fever. He was in bed for 4 days. He returned to work feeling well until 10 days before admission when he developed a nonproduc-

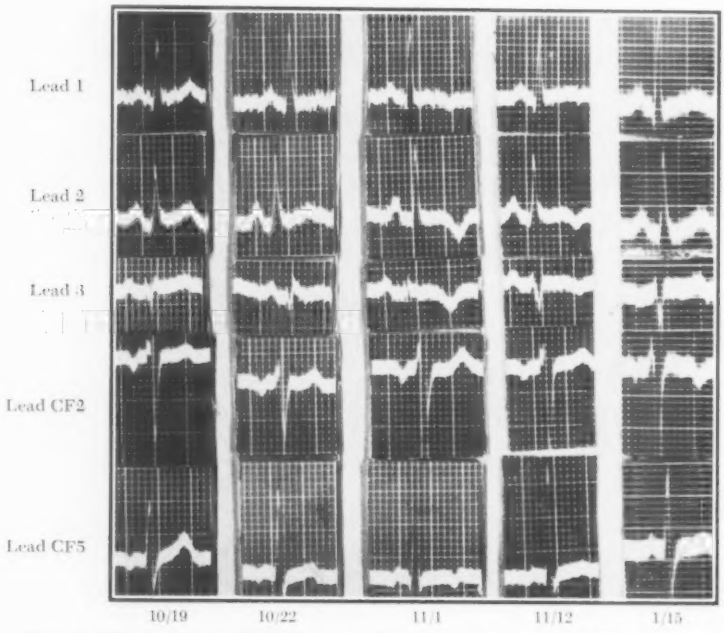

FIG. 5 (CASE 2).—Serial Electrocardiograms, Oct. 19, 1948, to Jan. 15, 1949.

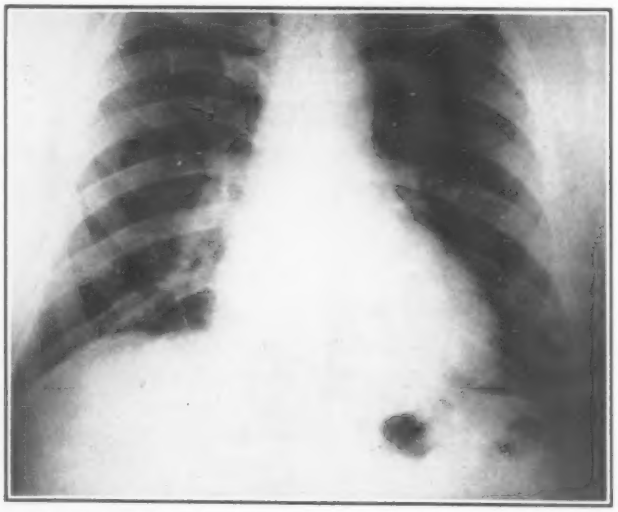

FIG. 6 (CASE 2).—Marked reduction in size of cardiac silhouette, Nov. 9, 1949.

tive cough and fever. Fever persisted, although the patient remained in bed for a full week receiving 300,000 units of penicillin and 6 gm. of sulfadiazine daily. Examination on admission showed an acutely ill man, perspiring profusely and not markedly dyspneic. A few moist rales were heard over the base of the left lung. A loud pericardial friction rub was audible. Roentgenogram of the chest (Fig. 4) showed an enlarged cardiac silhouette consistent with a diagnosis of pericardial effusion, and bronchopneumonia involving the lower lobe of the left lung. The electrocardiogram (Fig. 5) showed the pattern of acute pericarditis. Under symptomatic therapy the fever gradually subsided, reaching normal on the 5th day. The friction rub disappeared on the 3rd day. Repeated chest films (Fig. 6), the first and last of which are shown, showed a progressive diminution in the size of heart shadow and a resolution of the bronchopneumonia. Serial electrocardiograms (Fig. 5) showed progressive changes diagnostic of acute pericarditis. The RS-T intervals were at first elevated in the standard limb leads. This was followed by a flattening of T in Lead 1, then inversion of T in Leads 1, 2, 3, and CF5, and finally a return toward positivity of T in Leads 1 and CF5.

Laboratory Data. The white blood cell count on admission was 21,000 with 86% polymorphonuclear cells. During recovery it dropped to 10,000 with 72% polymorphonuclears. The sedimentation rate was 54 mm. per hour on admission and dropped to 28 mm. per hour prior to discharge. Agglutination tests against all known organisms, including cold agglutination, were negative. Blood culture was sterile. The antifibrinolysin titer was 4 +. The Mantoux test was negative.

Follow-up. Four weeks after discharge the patient complained of chilliness, sore throat and cough. Physical examination showed signs of an upper respiratory infection. The temperature was slightly elevated. He made an uneventful recovery and returned to work within a week. He has remained well since that time. An electrocardiogram taken 2 months after discharge (Fig. 5) was entirely normal.

Comment. There was no complaint of pain in this instance. Otherwise the clinical course, roentgenograms and electrocardiographic findings were typical of acute pericarditis. Associated pulmonary disease was present.

CASE 3. (No. 196415) F.P., a 52 year old white, married, female housewife was admitted to Beth El Hospital on May 10, 1949. There was a past history of bronchial asthma of 7 years' duration but the patient had been asymptomatic for 1 year prior to the present illness. A routine electrocardiogram (Fig. 8) taken Oct. 15, 1948, 7 months prior to the present illness, was normal. Two weeks before admission she was awakened from sleep with severe knife-like pain in the substernal region which radiated to the back of the neck, both shoulders and left arm. The pain was aggravated by respiration. The following day her temperature was 103°F. The pain persisted for 2 days. Despite administration of penicillin and sulfadiazine the temperature continued to fluctuate between 101 and 103°. The pain recurred intermittently and was very slight at the time of admission when the temperature was 100°, pulse 80, respirations 20, blood pressure 110/60. Examination of the heart disclosed distant heart sounds, an apical impulse which could not be palpated and a pericardial friction rub. The chest film (Fig. 7) showed the cardiac silhouette to be enlarged and small pleural effusions at both bases. The electrocardiogram (Fig. 8) showed T-wave changes consistent with a diagnosis of acute pericarditis of 2 weeks' duration. On symptomatic therapy the temperature gradually subsided and became normal on the 5th day. Three days later there was a spike to 101.4°, then a gradual fall to 100°, where it remained for the following 2 weeks. The pain was completely relieved after the first week. Repeated films of the chest (Fig. 9), the first and last of which are shown, showed a gradual decrease in the size of the heart shadow and absorption of the pleural effusion. Serial electrocardiograms (Fig. 8) showed a gradual return of the negative T waves toward positivity.

Laboratory Data. Blood counts showed hemoglobin varying from 68 to 75%, red blood cell counts from 3,200,000 to 3,700,000, white blood cell counts from 8,800 to 6,000 with a normal differential ratio, except that on 3 occasions the eosinophil counts were 9%, 5% and 4%. The sedimentation rate was 45 mm. per hour on admission and dropped to 30 mm. per hour prior to discharge. Urinalyses were negative. The blood culture was sterile. Agglutination tests against all the known organisms, including cold agglutination, were negative. Smears and cultures of sputa, gastric washings and stools were negative. The Mantoux test was positive in a dilution of 1: 10,000. A skin and muscle biopsy showed no evidence of vascular disease.

Follow-up. The patient has only recently been discharged from the hospital. She has

remained clinically well. No repeat studies have thus far been obtained.

Comment. This patient followed a typical course of acute primary pericarditis of unknown origin. The past history of asthma and the finding of eosinophilia on 3 occasions made it necessary to rule out diffuse vascular disease such as periarteritis nodosa. The absence of other clinical features and the negative biopsy eliminate this possibility. Associated pleural disease was present.

CASE 4. (No. 193656) I.M., a 40 year old married white laborer, was admitted to Beth El Hospital on Feb. 22, 1949, complaining of

FIG. 7 (CASE 3).—Pericardial effusion, bilateral pleural effusion, May 13, 1949.

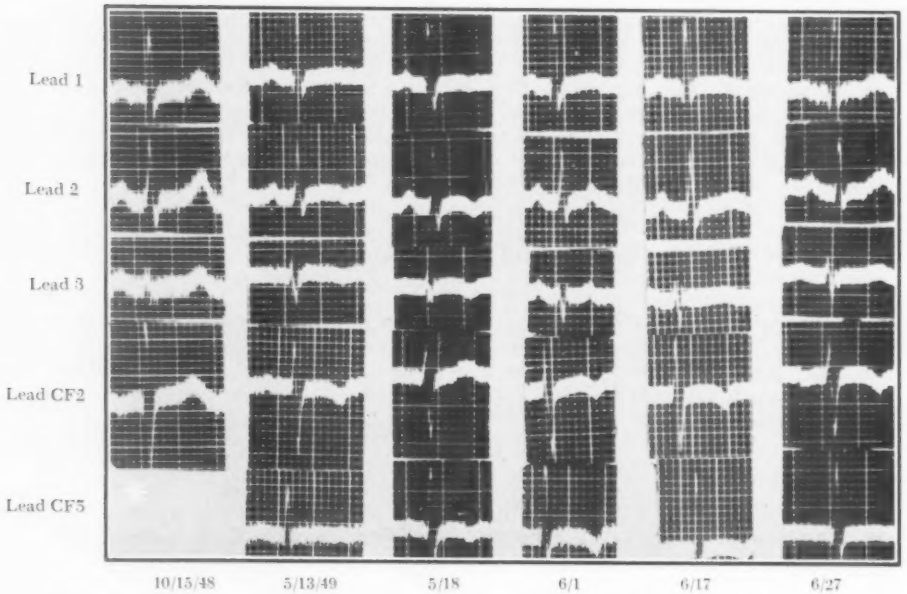

FIG. 8 (CASE 3).—Normal electrocardiogram 7 months prior to illness, Oct. 15, 1948. Serial electrocardiograms May 13, 1949, to June 27, 1949.

[6] Lead CF4

epigastric and precordial pain of 9 hours' duration. Four days prior to admission the patient was more fatigued than usual and had slight pain in the left axilla on deep inspiration. This was relieved by an analgesic on the following day. He returned to work. The night before admission the patient was awakened from sleep with severe sticking pain in the epigastrium and over the precordium which radiated toward the left axilla. There was difficulty in breathing, sweating and nausea. The history disclosed a similar attack of pain a year ago. This was diagnosed as a pleurisy. At that time he was well and able to return to work after one week of bed rest. Examination on admission disclosed a temperature of 101°, pulse 100, respirations 24 and blood pressure 140/90. Excursion of the left chest was limited and inspiratory rales were heard over the left lower lobe. A friction rub was audible along the left sternal border, synchronous with the heart sounds and unrelated to respiration. There was muscle spasm in the epigastrium. Roentgenogram of the chest was at first judged to be normal. However, in comparison with a subsequent film, measurements showed enlargement of the cardiac silhouette. Pleural thickening was seen at the left base. The electrocardiogram (Fig. 10) was diagnostic of acute pericarditis. Only symptomatic therapy was prescribed. On the 2d hospital day the temperature rose to 104°. The friction rub disappeared and returned a number of times. The temperature gradually subsided and became normal on the 5th day at which time the precordial and epigastric pain were completely relieved. Serial electrocardiograms (Fig. 10) showed the classical evolution of acute pericarditis. The RS-T segments were at first elevated in the standard limb leads. T was inverted in CF2 and diphasic in CF5. Eleven days later there was a return of the RS-T segments toward the isoelectric level and T was inverted in leads 1, CF2 and CF5. The patient signed a release on March 9 in order to return to work. He felt clinically well.

Laboratory data. Blood counts showed a hemoglobin of 88%, white blood cell count varying from 8,000 to 7,000, and polymorphonuclears from 66 to 60%. The sedimentation rate was 33 mm. per hour on admission and 14 mm. per hour on discharge. Agglutination tests against all the known organisms, including the cold agglutination test, were negative. Urinalyses were negative. Blood culture was negative. Smears and cultures of sputa and gastric washings were negative for tubercle bacilli. The Mantoux test was slightly positive in a dilution of 1: 100,000 and moderately positive in a dilution of 1: 10,000. The venous pressure, calcium gluconate and ether circulation times were normal.

FIG. 9 (CASE 3).—Normal chest film, June 21, 1949.

Follow-up. An electrocardiogram (Fig. 10) taken April 11, about one month after discharge, showed a complete reversion to normal. The patient at that time had no complaints. On May 26 there was a recurrence of substernal pain which was aggravated by breathing. Five days later the pain was relieved, but an electrocardiogram (Fig. 10) again showed the pattern of acute pericarditis. The patient returned to work. An electrocardiogram (Fig. 10) taken at our follow-up clinic on July 13 showed a normal pattern.

Comment. This case illustrates the recurrent nature of the attacks of acute pericarditis. The clinical course and electrocardiographic findings are typical. No etiologic factor is evident. No active acute or chronic lung disease is present. There was no preceding respiratory infection.

CASE 5. (No. 194779) R.D., a 22 year old male negro laborer, was admitted to Beth El Hospital on March 15, 1949, with complaints of a slight nonproductive cough, pain in the left lower chest and left upper abdominal quadrant of 1 week's duration. The onset of these symptoms was preceded by a head cold. The pain was intermittent and the patient continued to work. On the day of admission he felt chilly, the pain became more severe and it was aggravated by deep inspiration and movement of the body. The temperature was 99.8°, pulse 76, respirations 21 and blood pressure 130/85. Physical examination revealed limited expansion of the left side of the chest and occasional inspiratory rales in the left axilla. Roentgenogram of the chest was negative. The temperature dropped to 98.6° and the chest and abdominal pain subsided on the second hospital day. Three days after admission the patient stated he felt perfectly well. An electrocardiogram (Fig. 10) was then taken, but the patient was discharged before the report was received. It revealed elevated RS-T segments in Leads 1, 2 and CF5 and an inverted T in Lead CF5. The patient was recalled and readmitted for further observation on March 29. He had no complaints and was working during the week since his discharge. A repeat film of the chest was still negative. Serial electrocardiograms (Fig. 11) showed slight changes. On March 29, RS-T was still elevated in Leads 1 and CF5. T was isoelectric in Lead 2. On April 11, RS-T remained elevated in Leads 1 and CF5. T was more positive in Leads 1 and 2. The patient was asymptomatic and the temperature remained normal during his entire hospital stay. He was discharged on April 17.

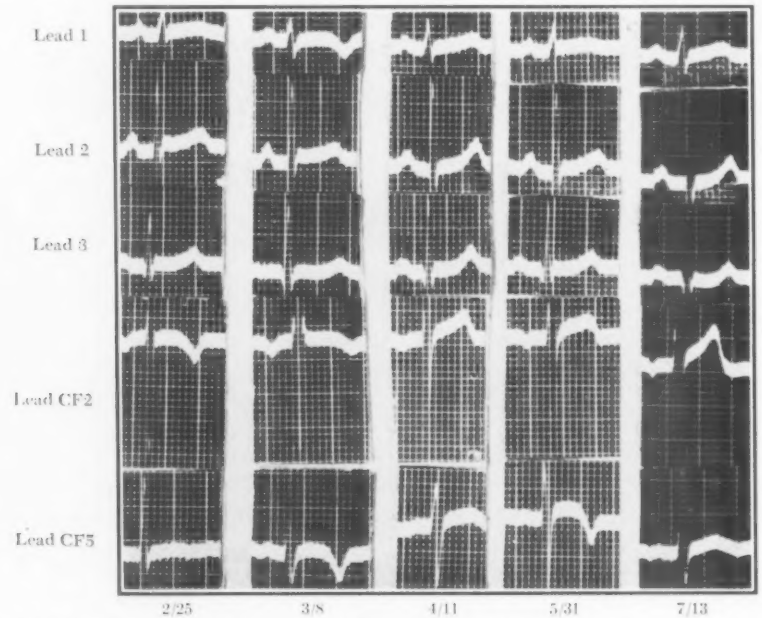

FIG. 10 (CASE 4).—Serial electrocardiogram during first illness, Feb. 25, 1949, to April 11, 1949. Recurrence, May 31, 1949. Normal, July 13, 1949.

Laboratory data. The blood count showed a hemoglobin of 80%, white blood cell count 7,300 with a normal differential smear. The sedimentation rate was 30 mm. per hour on admission and dropped to 7 mm. per hour on discharge. Urinalysis, blood chemical studies and Mazzini test were negative. The antifibrinolysin titer was 4+.

Follow-up. The patient was examined at our clinic on June 12, 1949. He remained well and was working since his discharge. Physical examination was negative. The electrocardiogram showed essentially the same changes as previously noted.

Comment. Although the clinical history was suggestive, no physical signs of pericarditis were present. There were no roentgenologic signs of pericardial effusion. No associated pulmonary disease was present. Only by means of a routine electrocardiogram was a diagnosis possible. After 3 months, electrocardiographic abnormalities are still present.

Discussion. The frequency with which we have encountered acute primary pericarditis of unknown origin since we have been on the lookout for it indicates that it is not a rare condition. Because of the usual mild and benign course during the acute episode, and the frequent association with respiratory infections which may distract our attention from the heart, it is probably more often missed than recognized. On occasion, because of incorrect electrocardiographic interpretation, it has been mistakenly diagnosed as acute coronary occlusion.

The etiology is unknown. In 4 cases in which pericardiocentesis was performed by Nathan and Dathe[10] the fluid was hemorrhagic and in no case were bacteria demonstrated on smears, cultures and guinea pig inoculation. Pericardial tapping was not indicated in any of our cases. All of the known

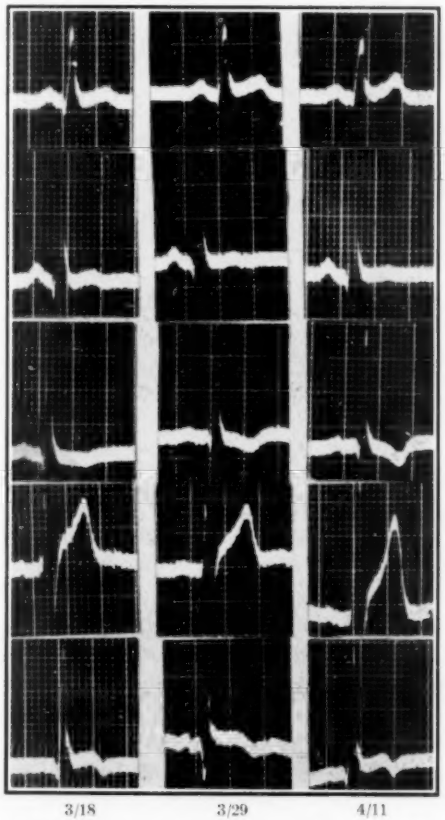

FIG. 11 (CASE 5).—Serial electrocardiograms March 18, 1949, to April 11, 1949.

agglutination reactions were negative. In all of our cases the cold agglutination test was negative. This suggests that if a virus is the etiologic factor it is not the same one that is responsible for primary atypical pneumonia.

The symptomatology is fairly characteristic. Pain is usually present. It was absent in one of our cases. The pain is substernal or precordial. In 2 of our cases the pain radiated to the abdomen. The pain is aggravated by breathing, swallowing, coughing and movement of the trunk. Dyspnea may or may not be present. Fever is not unusually high, although it reached 104° in 1 of our cases. Both fever and pain are usually shortlived, disappearing within about a week. Slight elevations of temperature may persist for a longer time. Recrudescence of symptoms may occur.

The physical examination was significant in 4 of our cases. A pericardial friction rub was audible in Cases 1 to 4. It however need not always be present and it may be evanescent in particular cases, being heard at one time and absent at another. Frequent examinations of the heart are necessary to be assured of its presence. Distant heart sounds, a paradoxical pulse and the inability to locate an apical impulse are suggestive findings. Signs of pulmonary or pleural involvement should not distract attention from the heart. Bronchopneumonia and pleural effusion were found in Case 1, bronchopneumonia in Case 3, and pleural effusion in Case 4. The concomitant presence of these conditions with the pericarditis, and their resolution as the pericarditis improved, suggest that the etiologic factor may be the same for both the pleuropulmonary and pericardial disorder.

The electrocardiographic and chest roentgenographic examinations establish the diagnosis. In the electrocardiogram early elevations of the RS-T segment followed by depressed and negative T waves, then a return of the RS-T segment to the isoelectric level and the T waves to positivity, are the classical features of the pattern in acute pericarditis. These changes persist for a longer interval than the clinical symptoms. In our Cases 1 to 4 they lasted for about 1 month. In Case 5 electrocardiographic changes are still present after a period of 3 months. In Coffen's case[5] RS-T changes persisted for as long as 6 months. The changes in size of the cardiac silhouette are characteristic.

Other laboratory data are not of diagnostic value. A rapid sedimentation rate was present in all of our cases. It gradually fell toward normal with subsidence of clinical activity. The blood count is not distinctive. Cases 1 and 4 had a moderate hypochromic anemia. Cases 1 and 3 showed a moderate leukocytosis (neutrophilosis). Case 4 had a slight eosinophilia, probably unrelated to the present illness. All other blood studies were essentially negative.

Differential diagnosis must be made from pericarditis secondary to or part of some other primary disease. Burchell[3] points out that pericarditis in rheumatic fever and tuberculosis is commonly painless and has a different clinical course. Pyogenic infections, renal insufficiency, diffuse vascular disease, and other causative mechanisms should easily be ruled out by adequate studies. Acute myocardial infarction may have to be distinguished from acute primary pericarditis of unknown origin. The absence of typical distribution of anginal pain, the aggravation of pain by breathing, swallowing, coughing or motion of the trunk, the presence of fever, pericardial friction rub and rapid sedimentation rate at the onset of acute non-specific pericarditis are clinical features which help differentiate both conditions

Changes in size of the cardiac silhouette and classical changes in serial electrocardiograms should leave no doubt as to the diagnosis. Recurrence of attacks, radiation of pain to the abdomen, muscular spasm and gastrointestinal symptoms may render the diagnosis difficult before confirmatory laboratory findings are available. In Case 1 a diagnosis of chronic gall bladder disease had been entertained for many months and the patient was admitted on the surgical service for an acute exacerbation of this condition.

There is no specific treatment. Chemotherapeutic and antibiotic agents seem to be of no value. Salicylates provide only slight symptomatic relief and do not shorten the course of the disease. Codeine affords relief of pain.

The prognosis for the acute attack is usually good. Only time and careful follow-up will tell whether any of these patients will ultimately develop constrictive pericarditis. Recurrent attacks are common. Cases 1 and 2 were observed by us to have definite recurrences. Perhaps in some of those instances of constrictive pericarditis, where an etiologic factor is not discernible, one or more unrecognized attacks of acute primary pericarditis may have previously occurred.

Only by paying close attention to mild or moderate precordial pain, occuring by itself or in association with respiratory infections, and availing ourselves of electrocardiographic and roentgenographic studies, will we be able to learn the true incidence of this kind of acute pericarditis. After the diagnosis is established, then only by careful observation of these patients over a period of years will we be able to learn whether serious sequelae may result.

Summary and Conclusions. 1. Acute primary pericarditis of unknown origin is a primary condition of the pericardium. No definite etiologic factor has been discovered, though respiratory lesions are frequently associated.

2. Careful attention must be paid to the complaint of substernal or precordial pain, especially in the presence of respiratory infections. Serial electrocardiographic studies and chest films will aid in the recognition of more of these cases.

3. Attacks are often recurrent. Careful observation of these patients for a period of years will determine the relationship of this disease to chronic constrictive pericarditis.

4. The literature has been reviewed. Five additional cases have been presented.

We wish to express our appreciation to Dr. E. W. Lipschutz and Dr. S. Gittelman for their kindness in permitting us to include their cases in this paper.

REFERENCES

1. **Barnes, A. R.,** and **Burchell, N. B.**: Am. Heart J., **23,** 247, 1942.
2. **Bellet, S.,** and **McMillen, T.**: Arch. Int. Med., **61,** 381, 1938.
3. **Burchell, H. B.**: Mod. Concepts Cardiovasc. Dis., **16,** 203, 1947.
4. **Cecil, L.**: Text Book of Medicine, 7th ed., Philadelphia, W. B. Saunders, 1947.
5. **Coffen, C. W.,** and **Scarf, M.**: Am. Heart J., **32,** 515, 1946.
6. **Finkelstein, D.,** and **Kleiner, M. J.**: Am. Heart J., **28,** 385, 1944.
7. **Harrington, S. W.**: Ann. Surg., **120,** 468, 1944.
8. **Levine, S. A.**: Clinical Heart Disease, 3d ed., Philadelphia, W. B. Saunders, 1947.
9. **Logue, R. B.,** and **Wendkoss, M. H.**: Am. Heart J., **36,** 587, 1948.
10. **Nathan, D. A.,** and **Dathe, R. A.**: Ibid., **31,** 115, 1946.
11. **Smalley, R. E.,** and **Ruddock, J. C.**: Ann. Int. Med., **25,** 799, 1946.
12. **Sprague, H. B.,** and **White, P. D.**: Med. Clinics No. Am., **15,** 900, 1932.
13. **VanderVeer, J. B.,** and **Wagner, J. A.**: Clinics, **5,** 96, 1946.
14. **White, P. D.**: Heart Diseases, 3d ed., New York, Macmillan, 1944.
15. **Willius, F. A.**: Proc. Staff Meet. Mayo Clinic, **9,** 637, 1934.
16. **Wolffe, L.**: New England J. Med., **230,** 422, 1944.

THE DOSAGE-RESPONSE CURVE FOR THE COMPARISON OF MERCURIAL DIURETICS*

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The dosage-response curve has become a standard device for the comparison of drugs in animals[2]. Such curves provide not only quantitative, but qualitative information concerning agents in a comparison. This technique for ascertaining the relative potency of drugs, and any qualitative difference which may exist, is not generally utilized in the study of drugs in man. This may account for the discordant results regarding the potency of agents in humans often seen in the clinical literature. The use of a dosage-response curve is in principle similar to that of calibration curves in other scientific measurements; for example, the curve of color change of an indicator of hydrogen-ion concentration. In the latter curve there is a middle sensitive portion in which a small change in the pH produces a marked change in tint, while at the 2 extremes, the curve is much less sensitive and large changes in the pH produce only small or undetectable changes in the tint. The same is true when chemical agents are tested biologically. Here also there is a sensitive range in which a small change in dose or concentration is revealed by a large response, and there are relatively insensitive ranges at the 2 extremes where large changes in the dose or concentration produce little or no change in response. If 2 drugs are compared in doses which lie at the extremes of the dosage-response curve, differences between them may escape detection, or the values representing the difference may prove misleading. The clinical literature provides innumerable examples of error in the relative potency of drugs by reason of the fact that, in the absence of a

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dosage-response curve, the comparisons were made in the insensitive range of dosage, or by the method in which equal doses were given, and the ratio of the effects was taken to represent the relative potency of the drugs. The fallacy of the latter method may be illustrated by data taken from a recent study[4], in which the potencies of cinchona alkaloids were compared with respect to their effects on the rate of the fibrillating auricle in man. As seen in Table 1, a dose of 0.4 gm. of quinine slowed the rate by 10%, 0.8 gm. slowed the rate by 20% (doubling the dose doubled the effect), and a dose of 1.2 gm. slowed the rate by 30%. A dose of 2.0 gm., however, produced no greater effect, indicating that doses above 1.2 gm. lay outside the sensitive range of response to this drug. In the same study, a dose of 0.4 gm. of quinidine slowed the rate by 20%, which taken by itself, would indicate that quinidine was 100% more potent than quinine. A dose of 1.2 gm. of quinidine, however, slowed the rate by 40%, as against 30% for a similar dose of quinine, and this, taken by itself, would indicate that quinidine was only about 30% more potent than quinine. This clearly shows that the relative potency of the 2 drugs cannot be established from differences in effects produced by similar doses. Valid ratios of potency can only be obtained from differences in doses which produce similar effects, and the device for this is the dosage-response curve.

TABLE 1.—SHOWING THE FALLACY OF ASSUMING RELATIVE POTENCY OF DRUGS FROM THE RATIO OF EFFECT PRODUCED BY SIMILAR DOSES

Quinine		*Quinidine*		
Dose (gm.)	*Per cent slowing of auricular rate*	*Dose (gm.)*	*Per cent slowing of auricular rate*	*Ratio of potency*
0.4	10	0.4	20	1:2
0.8	20			
1.2	30	1.2	40	1:1.3
2.0	30			

The scarcity of dosage-response curves in the comparison of drugs in man was brought to our attention vividly by the recent clinical studies of the new mercurial diuretic, thiomerin[1,3]. In these, the potency of the compounds was compared in terms of the diuretic effect produced by similar doses. They present no evidence as to whether the doses lay in the steep or in the flat portions of a dosage-response curve, and therefore provide no means of ascertaining the validity of the values concerning relative potency.

The present report deals with data which show the feasibility of a dosage-response curve in the comparison of mercurial diuretics in man. A preliminary account of such experiments was published in 1946[5].

The subjects were a group of 73 ambulant patients with congestive failure in attendance in our cardiac clinics. The procedure was as follows: the patient was weighed, a dose of the mercurial diuretic was injected intravenously, and the patient weighed again 15 hours later. The difference between the 2 weights represented the diuretic effect of the dose, in addition to a small loss of weight which normally occurs during the night (an average of 0.89 lb. established by 115 trials in 35 of these patients). One week

later the patients returned to the clinic. During this time the weight that had been lost was almost invariably regained. For example, the group of 56 patients which received 1 cc. had an average weight of 151.4 ± 30.0 lbs., and on their visit a week later, their average weight had returned to 151.8 ± 30.1 lbs. The diuretic agent was mercuhydrin, and the doses ranged from 0.25 to 2.5 cc.

The results are summarized in Table 2. The normal overnight weight loss was subtracted from the total loss for each dose to obtain the average loss due to mercuhydrin. The standard deviation of the average weight loss from each dose is an estimate of the

TABLE 2.—RESPONSE TO 971 INTRAVENOUS INJECTIONS OF MERCUHYDRIN IN 73 PATIENTS WITH CONGESTIVE FAILURE

Dose (cc.)	*No. of patients*	*No. of doses*	*Average weight loss (lbs.)*	*Standard deviation of the average weight loss*	*Weight loss due to mercuhydrin (lbs.)*
Control	35	115*	0.89	0.12	—
0.25	46	46	0.77	0.16	−0.12**
0.50	55	83	2.44	0.24	1.55
0.75	49	59	2.70	0.35	1.81
1.00	56	296	3.50	0.13	2.61
1.25	33	33	4.20	0.42	3.31
1.50	35	36	3.72	0.48	2.83
1.75	35	37	4.20	0.35	3.31
2.00	49	210	4.69	0.20	3.80
2.25	34	34	4.82	0.34	3.93
2.50	20	22	4.51	0.62	3.62

* This value represents the number of weighings after the injection of an inert material.
** The average response to 0.25 cc. was less than the average weight loss in the control.

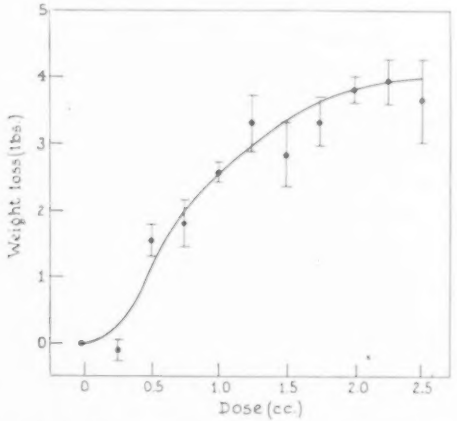

FIG. 1.—A typical "S"-shaped dosage-response curve, with steep or sensitive range in the central portion. The points indicate the average weight loss for each dose of mercuhydrin; the vertical lines through the points, the range of the standard error of the average for each dose. The curve indicates that the most responsive range lies between doses of 0.5 and 2.0 cc., and that for most patients larger doses, which lie in the "ceiling" area of the curve, are not likely to produce significantly greater effects.

reliability of the result. The average weight loss for each level of dosage was plotted in 2 ways. In Fig. 1, the weight loss was plotted against the dose. This shows the typical "S"-shaped curve with the steep, or sensitive, part in the range of doses from 0.5 to 2 cc., representing average weight losses of from 1.5 to 3.75 lbs. respectively. The curve is flatter at the lower dose level, and reaches a "ceiling" at above 2.0 cc., suggesting that there is little value in giving larger doses to ambulant patients with congestive failure. In Fig. 2, the same data are presented in a curve in which the weight losses are plotted against the dose on a logarithmic scale. This provides a straight line, which represents the usual relationship between the doses of a drug and the corresponding responses, and is more suitable for the comparison of the potency of drugs.

Summary and Conclusions. 1. Comparisons of mercurial diuretics in man by the conventional method in which differences in diuretic effects with similar doses of the agents are used as a means of deciding relative potency are not sound. Valid comparisons require the use of dosage-response curves.

2. It is feasible to prepare satisfactory dosage-response curves for mercurial diuretic agents in patients with congestive failure.

3. A dosage-response curve for mercuhydrin is presented.

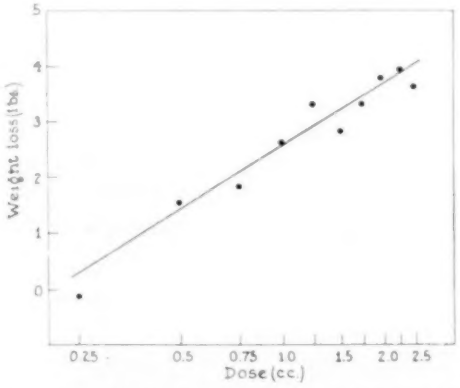

FIG. 2.—Linear dosage-response relationship when the points on the "S"-shaped curve of Fig. 1 are plotted against the log of the dose. This type of curve is especially useful for comparing the relative potency of drugs.

REFERENCES

1. **Batterman, R. C., Unterman, D.,** and **DeGraff, A. C.:** J. Am. Med. Assn., **140,** 1268, 1949.
2. **Bliss, C. I.,** and **Cattell, McK.:** Ann. Rev. Physiol., **5,** 479, 1943.
3. **Herrmann, G. R., Chriss, J. W., Hejtmancik, M. R.,** and **Sims, P. M.:** Texas J. Med., **45,** 79, 1949.
4. **Modell, W., Shane, S. J., Dayrit, C.,** and **Gold, H.:** Proc. Fed. Am. Soc. Exp. Biol., **8,** 320, 1949.
5. **Modell, W., Gold, H.,** and **Clarke, D. A.:** Ibid., **5,** 193, 1946.

THE DISTRIBUTION OF RADIOMERCURY OF A MERCURIAL DIURETIC IN SOME OF THE BODY FLUIDS OF MAN*

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During the course of experiments[2,3,5,6,9] with Mercuhydrin† labeled with $Hg^{203,205}$, various body fluids were obtained for the purpose of studying the relationship of the concentration-time course of the radiomercury in the blood serum to that in the respective body fluids. All of the various fluids could not be studied in the same subject nor could they be studied comprehensively in many instances.

Many observations on the distribution and excretion of mercury are found in the literature[4,7,8]. However, these investigations have been concerned principally with mercury in the treatment of syphilis by inunction or injection or with mercurial poisoning. These constitute a different problem from that of an intravenously administered mercurial diuretic in that the factors of time, total dosage, rapidity of absorption, and the chemical compound containing the mercury affect its distribution and excretion. In view of the relative paucity of data on the distribution and fate of the mercury incorporated in a mercurial diuretic of the type used frequently in clinical medicine, it seems advisable to report these observations, even though the series is small and the data were obtained only incidentally to other more extensively planned investigations.

Materials and Methods. The subjects were adults who were either normal or were suffering with disease states which produced pleural, peritoneal, or edema fluids suitable in quantity for collection and study. Two cubic centimeters of the mercurial diuretic was administered intravenously, each cc. containing 39 mg. of mercury. The radiomercury had an activity such that 8 to 20 million counts per minute were introduced. In an occasional instance, the diuretic was introduced in a capsule, as previously described[6]. When possible, samples of the body fluids were collected simultaneously with those of blood, for purposes of comparison.

The various body fluids were collected in the following manner:

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† The Mercuhydrin (methoxy-oxymercuripropylsuccinylurea with theophylline labeled with radiomercury) was prepared in this laboratory by Messrs. Harold Krahnke, Darwin Kaestner, and Edwin Sprengler through the cooperation of Dr. H. L. Daiell of Lakeside Laboratories, Milwaukee, Wisconsin.

1, gastric juice by means of a stomach tube in one subject;

2, sweat in vials, from the surfaces of the body of 9 subjects who rested quietly in a hot and humid room (approximately 49° C. and 75% relative humidity). The subjects entered the hot room at varying lengths of time after the injection (0-120 minutes);

3, bile from the outlet of a T-tube placed in the common bile duct for postoperative

TABLE 1.—CLINICAL DATA

Material Studied	*No. of Subjects*	*Sex* M	F	*Color* C	W	*Age or Age Range (Yrs.)*	*Diagnoses*
Ascitic fluid	2	2		1	1	58 & 60	2 Hepatic cirrhosis
Sputum	3	2	1	3		41 – 68	1 HCVD* with CHF** 1 ASHD*** with CHF** 1 Cholecystitis
Pleural fluid	2	1	1	2		16 & 58	1 Tuberc. with pleural effusion 1 Malignancy and scleroderma
Gastric juice	1	1		1		31	1 Postpneumonia
Pericardial fluid	1	1		1		68	1 Tuberc. pericard.
Sweat	9	6	3	9		24 – 54	3 Gastric neuroses 3 Peptic ulcers 1 Unresolved pneumonia 1 Hypertrophic arth. 1 Gonococcal arth. (recovered)
Erythrocytes	9	6	3	9		22 – 59	3 Syph. aort. insuffic. with CHF** 1 Asthma with cor pulmonale and CHF** 1 RHD**** with CHF** 1 Pylorospasm 1 ASHD*** with CHF** 1 Pneumonia 1 Hepatic cirrhosis
Spinal fluid	4	4		4		19 – 36	1 Pulmonary abscess 1 Hepatitis 1 Infectious mononucl. 1 Pneumonia All convalescent
Edema fluid	16	11	5	14	2	33 – 76	5 HCVD* with CHF** 3 Syphil. heart dis. with CHF** 1 Lymphatic obstr. 5 ASHD*** with CHF** 1 Chronic glomerulonephritis with nephrotic syndrome 1 RHD**** with CHF**
Injection into ascitic fluid	5	3	2	3	2	56 – 84	4 Hepatic cirrhosis 1 Carcinoma of stomach with peritoneal metastases
Bile	4		4	1	3	32 – 55	1 Biliary calculi 2 Postop. cholecystectomy 1 Biliary fistula (repaired)

* Hypertensive cardiovascular disease
** Congestive heart failure
*** Arteriosclerotic heart disease
**** Rheumatic heart disease

drainage in 4 subjects and from the gallbladder in 1 subject;

4, cerebrospinal fluid by means of lumbar puncture in 4 subjects;

5, edema fluid by means of a 20-gauge needle as used for muscle tissue pressure[1] inserted into the tissue spaces of 16 subjects;

6, ascitic fluid by paracentesis in 2 subjects;

7, saliva by expectoration in 4 subjects;

8, pleural fluid by thoracentesis in 2 subjects;

9, pericardial fluid by paracentesis in 1 subject; and,

10, erythrocytes separated from the plasma and then washed twice with a physiologic solution of sodium chloride in 9 subjects. Clinical data concerning the subjects studied are summarized in Table 1.

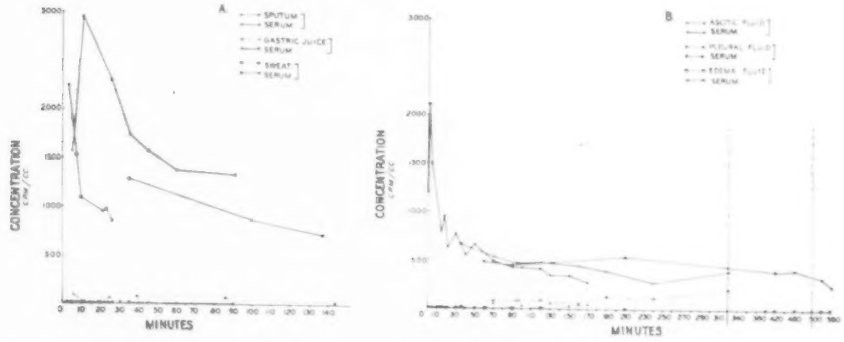

FIG. 1.—Distribution of radiomercury in various body fluids. The measurements were made on different subjects. *(A)* Relative concentrations of radiomercury in the serum, gastric juice, sputum and sweat of 3 subjects. *(B)* Relative concentrations of radiomercury in the serum, ascitic fluid, pleural fluid, and edema fluid of 3 subjects.

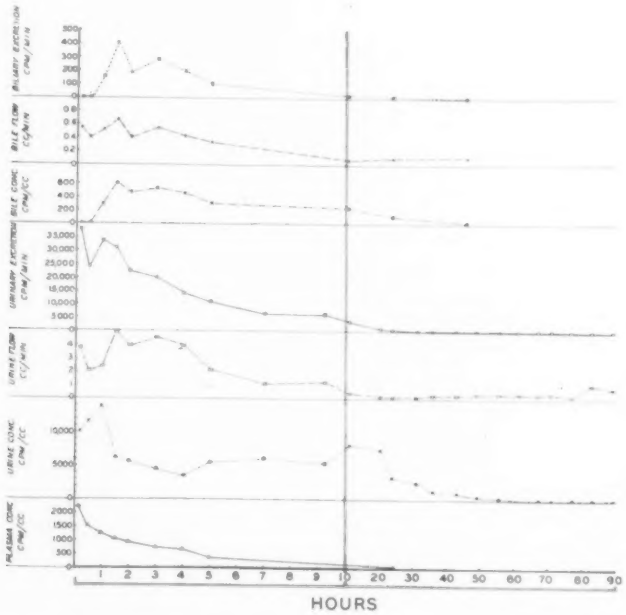

FIG. 2.—Relative concentration of radiomercury in the serum, urine and bile of 1 subject, a 49 year old colored woman with cholelithiasis and T-tube drain.

Results. Results are summarized in Figs. 1, 2 and 3. It is evident from these illustrations that the radiomercury did not escape in high concentrations into the body fluids studied, with the exception of bile. The escape into sweat and gastric juice was essentially zero and was slow into edema fluid, sputum, ascitic fluid, and pleural fluid (Fig. 1A and B). On the other hand, the escape into bile was relatively high, though it did not reach the levels encountered for the urine (Fig. 2). The bile of 2 of the subjects was studied quantitatively for total excretion of radiomercury; in one, 7.2% of the recovered radiomercury administered orally was in the bile; 92.8% was in the urine, and in the other, 2.7% of the intravenously injected dose was excreted in the bile and 94.2% in the urine. Relative rates of excretion in the urine and bile are shown in detail in Fig. 2.

No accumulation of radiomercury was detected in the spinal fluid. Absence of transfer of measurable quantities of radiomercury into the spinal fluid was consistent for all subjects studied. The washed erythrocytes did not contain any of the isotope. The two washings could have removed radiomercury that may have been adsorbed or bound to the surfaces of the erythrocytes.

The other fluids, on the other hand, showed wide variations from subject to subject; the illustrations shown represent typical patterns. Even though the concentration varied considerably in the time-course, all the fluids except urine, blood, and bile were consistently low in concentration by comparison.

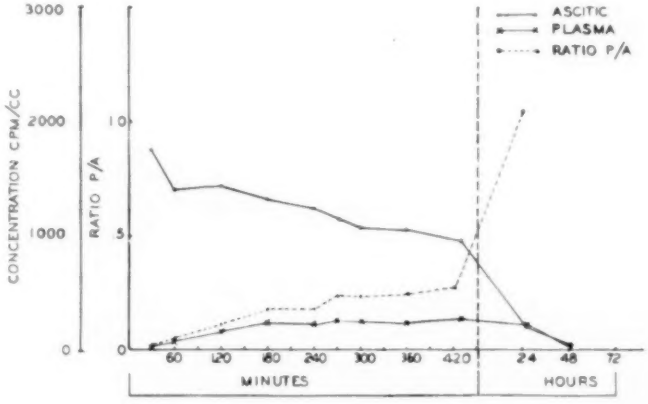

FIG. 3.—Relative concentrations of radiomercury in the plasma and ascitic fluid after intraperitoneal injection in a 53 year old white woman with Laennec's cirrhosis. The ratio of concentration of plasma to concentration of ascitic fluid is shown. The slow appearance in the plasma is apparent, 24 hours being required before the concentrations are the same.

Each of 6 subjects with ascites received 2 cc. of the labeled diuretic intraperitoneally. Results are typified by the example shown in Fig. 3. There were wide variations in absolute values of the concentrations in the blood serum and ascitic fluid which are explainable by differences in the volume of ascitic fluid among patients. All subjects showed a definite absorption of the material from the peritoneal space. One subject had none remaining in the ascitic fluid at the end of 24 hours, whereas another, followed for

72 hours, still showed significant quantities. Most of the radiomercury was excreted in the urine.

Discussion. Since the movement of the radiomercury is a direct index of the movement of all of the mercury in the diuretic, and since there is relatively little mercury in the entire body of man, the data represent quantitatively as well as qualitatively the distribution of the mercury of a mercurial diuretic administered intravenously[9]. In one subject who received the labeled diuretic orally the pattern of the concentration-time course for the radiomercury in the bile was not significantly different from that presented in the bile by the other subjects who received the material intravenously.

The quantitative distribution of the radiomercury was not extensive, being limited primarily to the blood, urine, bile, and feces. Failure of mercury to penetrate readily the vascular barriers may be due to its tendency to be fixed fairly firmly to the protein molecules of the plasma. The rapid unidirectional removal of the mercury from the blood by the kidneys with excretion into the urine is probably responsible in part for failure of the element to enter slowly the other body fluids and reach relatively high concentrations therein.

In many of the studies counts of samples were frequently 10 to 20 above background (16 to 24 counts per minute). Such sporadically appearing values were most probably the result of statistically expected variations in counting and technique. For example, when tissue fluid is collected and a needle puncture is made, spillage of minute amounts of blood might produce such variations, especially during periods when the concentration of radiomercury in the blood is high. Although such variations are shown in the illustrations, only those points which exhibit a consistent trend can be considered significant. A good example of this type of curve is represented by that for the pleural fluid (Fig. 1). Regardless of the possible errors due to statistical factors concerned with counting and spillage of blood into the body fluids during this collection, the data indicate definitely a slight transfer of the mercury of an intravenously administered mercurial diuretic out of the blood vessels.

Data for feces are not shown because of the difficulties and uncertainties of the method from a quantitative point of view. Concentration of the radiomercury in the feces varied with its quantity and physical state. A larger amount of mercury was excreted in the feces when diarrhea existed. Furthermore, because a specimen was not passed daily, calculations of rate of excretion were disturbed. Approximately 0.01 to 26% of the intravenously administered diuretic was recovered in the feces. This has been discussed previously[4,8] for oral administration of the diuretic.

Contrary to previous reports, the sweat glands, unlike the kidneys, were found not to excrete measurable amounts of the mercurial diuretic[8]. The same is true for the glands of the stomach.

Failure of mercury to accumulate in the tissues in relatively large amounts in general arouses speculation concerning the diuretic action of the material through systemic action, although the action of a drug is not *necessarily* directly related to its concentration in a tissue.

The relatively high concentration of mercury in the bile, as compared with other body fluids, except blood and urine, is in essential agreement with previous studies. However, the total amount excreted in the bile is rela

tively small—2.7% in one patient. The ratio of concentration of mercury in the bile to that found in the urine and blood depends in large part on the time of sampling (Fig. 2). Thus with collections made 6 to 20 hours after injection, when the blood content of mercury was low, the concentration of bile was greater than that of the blood. Such factors as the slow rate of biliary flow and relatively low rate of clearance of mercury by the liver, as well as the large storage space in the liver and relatively slow elimination of mercury from these stores, must be evaluated. It is apparent that biliary excretion of the mercury of a mercurial diuretic is not an important route of elimination in the presence of normal kidneys. With impaired renal function and good hepatic function, biliary excretion appeared to be more significant in one subject.

Summary. The distribution of radiomercury in edema fluid, ascitic fluid, pleural fluid, bile, saliva, gastric juice, cerebrospinal fluid, sweat, and erythrocytes following intravenous administration of a single dose of a mercurial diuretic is described. No measurable quantities entered the cerebrospinal fluid, sweat, gastric juice and erythrocytes, and only low concentrations were reached in the saliva, edema, peritoneal and pleural fluids. Relatively high concentrations were attained in the bile.

We wish to acknowledge the assistance of Drs. W. H. Gordon and W. J. Overman in these studies. The following senior students participated in the sweat studies: Alton Ochsner, Jr., Lee Garlett, Chapman Bertinot, and James Hendrick.

REFERENCES

1. **Burch, G. E.**, and **Sodeman, W. A.**: J. Clin. Invest., **16**, 845, 1937.
2. **Burch, G. E., Ray, C. T., Threefoot, S. A., Kelly, F. J., Harp, V. C.**, and **Svedberg, A. H.**: The Urinary Excretion and Biologic Decay Periods of Radiomercury Labeling a Mercurial Diuretic in Normal and Diseased Man. In press.
3. **Kelly, F., Svedberg, A. H.**, and **Harp, V. C.**: The Transfer of Radioactive Mercury Across a Membrane Produced by the Application of Cantharides to the Skin of Man. In press.
4. **Lomholt, S.**: Brit. J. Dermat. and Syph., **32**, 353, 1920.
5. **Milnor, J. P., Burch, G. E., Ray, C. T., Threefoot, S. A.**, and **Berenson, G. S.**: J. Clin. Invest., **24**, 72, 1950.
6. **Overman, W., Gordon, W. H.**, and **Burch, G. E.**: Tracer Studies of the Urinary Excretion of Radioactive Mercury Following Oral Administration of a Mercurial Diuretic, Circulation. In press.
7. **Ray, C. T.**, and **Burch, G. E.**: Am. J. Med. Sci., **217**, 96, 1949.
8. **Sollman, T.**: A Manual of Pharmacology, 6th ed., Philadelphia, W. B. Saunders, 1942.
9. **Threefoot, S. A., Ray, C. T., Burch, G. E., Cronvich, J. A., Milnor, J. P., Overman, W.**, and **Gordon, W. H.**: J. Clin. Invest., **28**, 661, 1949.

STUDIES ON THE USE OF AUREOMYCIN IN HEPATIC DISEASE*
III. A NOTE ON AUREOMYCIN THERAPY IN HEPATIC COMA

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In addition to numerous supportive measures, aureomycin was given to 4 patients in acute liver failure with coma. In 2 instances the liver failure complicated viral hepatitis; in the other 2, portal cirrhosis. In the experience of most observers, the mortality rate in cases of hepatic coma, particularly following viral hepatitis, has been very high despite many types of supportive treatment. Thus it was very encouraging to observe 4 consecutive cases of acute hepatic coma who showed improvement upon receiving aureomycin in addition to supportive therapy. In 2 of these the improvement was immediate and striking. Although it is not possible to draw any conclusions from this small number of cases, the results were sufficiently encouraging to warrant this report. The case histories of the 4 patients are as follows:

Case Reports. Case 1. This 6 year old white girl was found to have chronic myelogenous leukemia in September, 1948, when she was studied because of a sore throat, fever, and systolic apical murmur. She had a white blood cell count of 97,000 with immature cells, and bone marrow examinations verified the diagnosis. Clinically the patient was asymptomatic and was in an apparent remission. Physical examinations at regular intervals between September, 1948, and 2 February, 1949, were negative except for a slightly enlarged spleen. The liver was never palpable or tender during this period. The patient did not receive any transfusions of whole blood or any blood products. She did have numerous venipunctures for diagnostic procedures. On 2 February, 1949, a routine count done in the Hematology Clinic of The Children's Hospital of Philadelphia revealed a hemoglobin of 9 gm. and a white blood cell count of 60,000, which was similar to counts made during the preceding 5 months.

On 4 February, 1949, the patient developed anorexia, malaise, nausea, vomiting, and right upper quadrant abdominal pain which persisted until admission on 12 February, 1949. Scleral icterus was first noted on 8 February, 1949. The patient rapidly became more jaundiced and was intensely so on the day of admission. The patient's mother noted that the child had slept almost continuously for 2 to 3 days before admission, but had been rational and well oriented when awakened. On 11 February, 1949, the patient had a nose bleed and vomited blood which she apparently had swallowed. She was admitted to The Children's Hospital at 3 a. m. on 12 February, 1949.

* This work was supported by the Commission on Liver Diseases of the Armed Forces Epidemiological Board, Preventive Medicine Division, Office of the Surgeon General, Washington, D. C.

Physical examination on admission revealed a pale, jaundiced, slender, 6 year old white girl who was somewhat irritable but in no acute distress. Clotted blood was found in her nose and posterior nasopharynx. Abdominal examination revealed a smooth, firm, tender liver, extending 5 cm. below the right costal margin. The lower edge of the spleen was felt about 5 cm. below the left costal margin. The patient was well oriented and the remainder of the physical examination was not abnormal. About 7 days after admission coma rapidly developed. She was completely unresponsive and her pupils were dilated and responded sluggishly to light. A spinal tap at this time yielded clear fluid with normal pressure and 20 mg. protein per 100 ml. On the day of admission, urinalysis was negative, except for the presence of bilirubin. It was negative for urobilinogen. The urine pH was 5 and specific gravity 1.023. Her hemoglobin was 5.7 gm. and her white blood cell count was 129,000 with 88% neutrophils, about half of which were immature forms, 9% lymphocytes, and 3% eosinophils. Two normoblasts were seen per 100 leukocytes. The platelet count was 30,000; bleeding time, 1 minute; venous coagulation time, 5 minutes (Lee and White), and clot retraction normal. The liver function studies were as follows: Total serum bilirubin, 19.98 mg. per 100 ml.; 1 minute direct-reacting bilirubin, 10.14 mg. per 100 ml.; thymol turbidity, 7.1 units; thymol flocculation, 3+; cephalin-cholesterol flocculation ± in 24 hours, and 4+ in 48 hours; and colloidol red, 4+.

The diagnosis made was acute viral hepatitis with coma superimposed upon a chronic myelogenous leukemia. The diagnosis of viral hepatitis was based on the following: 1, The history was quite typical of viral hepatitis with onset on 4 February, 1949; 2, an enlarged, tender liver which had not been present previously; 3, an intense jaundice in absence of evidence of extensive hemolysis or biliary obstruction; 4, the liver function studies indicating acute hepato-cellular damage; and 5, her subsequent hospital course.

Treatment. Aureomycin, 100 mg. every 6 hours intramuscularly, was given from 12 February, 1949, to 18 February, 1949, when a change to oral aureomycin, 250 mg. every 6 hours, was made. The oral aureomycin was stopped on 3 March, 1949. The patient received 500 cc. of blood on 12 February, 1949, and daily plasma infusions for 1 week. She was given large doses of vitamin K and other vitamins parenterally. She received intravenous glucose solutions for 1 week and was given a high protein, high carbohydrate diet as soon as it was tolerated.

Course in Hospital. Twenty-four hours after lapsing into coma and after the onset of aureomycin therapy the patient was mentally alert and well oriented. She appeared somewhat less jaundiced, the liver was less tender, and appeared to be smaller. Some coarse rhonchi were heard in the bronchi, and a single dose of both crystalline and procaine penicillin was given. Forty-eight hours after admission the patient again became lethargic and semicomatose and remained so most of the day. However, on the following day she was again mentally alert and responsive and remained so. The liver and spleen remained unchanged to physical examination during this second episode of coma. From the 3rd day, the patient's course was one of steady improvement. The liver size and tenderness gradually diminished and the jaundice subsided. The liver function studies had practically returned to normal in 1 month. She rapidly regained her weight and strength and at time of discharge was in the same physical condition as at the onset of the hepatitis. Her chronic myelogenous leukemia continued as previously with hemoglobin of 9.5 gm. and white blood cell count of 65,000, with 87% mature and immature neutrophils, 5% lymphocytes, 3% monocytes and 5% eosinophils.

Case 2. This 10 year old white girl was admitted to the Chester Hospital on 4 November, 1948. The illness began 5 days before admission with headache and fever up to 105° F., followed by repeated vomiting. These complaints became more severe and, in addition, marked prostration and right upper quadrant abdominal pain developed. Intramuscular penicillin was given every 3 hours for 5 days before admission without any beneficial effect.

Physical examination on admission revealed a profoundly prostrated, mentally sluggish, and mildly cachectic girl weighing 35 kg. She was vomiting or retching almost constantly and was quite jaundiced. Her temperature on admission was 99.6° F. The liver edge extended 1 cm. below the right costal margin in the mid-clavicular line and was smooth, firm, and quite tender. There were no other abnormal physical findings.

Urinalysis revealed excessive amounts of bilirubin and urobilinogen, but was otherwise not abnormal. Her hemoglobin was 13 gm., Rbc 4.6 million, Wbc 5,400 (neutrophils 61%, lymphocytes 39%). Her total serum bilirubin was 23 mg. per 100 ml., icterus index 100 units, positive direct and indirect Van den Bergh reaction, 2+ cephalin-cholesterol floc-

culation test, fasting blood sugar 135 mg. per 100 ml. and blood urea nitrogen 12 mg. The spinal fluid was clear with no cells, no growth on culture, protein 10 mg. per 100 ml., chlorides 740 mg., sugar 108 mg., and a normal colloidal gold test. No spirochetes were found on darkfield examination of the urine. Roentgenograms of chest and skull revealed nothing abnormal. An agglutination test for Weil's disease on 15 November, 1948, was negative. A blood culture taken on 10 November and 20 November, 1948, yielded no growth. A heterophil antibody test on 21 November, 1948, was positive only to a dilution of 1:28. The total serum protein was 7.8 gm. % on 20 November, 1948.

The temperature remained between 101° and 103° F. during the first 48 hours after admission, and her jaundice became more intense. About 5 days after admission the child became semi-comatose with nuchal rigidity, hyperactive deep reflexes, rigid lower extremities, and bilaterally positive Babinski reflexes. The lower edge of the liver was at the level of the umbilicus and very tender. The Wbc rose to 24,000 with little change in the differential count. During the next week the coma deepened and the child became more cachectic despite institution of gavage feedings.

Penicillin, 50,000 units every 3 hours intramuscularly, and sulfadiazine, 0.5 gm. every 4 hours orally, were given from 7 November to 15 November, 1948. On the 14th hospital day, 17 November, 1948, aureomycin was started. It was first given intramuscularly, 75 mg. every 8 hours, until 2 December, 1948, when 250 mg. were given orally every 4 hours and continued to 15 January, 1949.

The child appeared to be in a terminal state when aureomycin was started, but began to show clinical and laboratory evidence of improvement about 2 weeks after the onset of aureomycin therapy. The jaundice disappeared, the abnormal central nervous system manifestations subsided, and her strength, general appearance, and appetite improved markedly. On 11 December, 1948, she was alert, asymptomatic, and was eating well. Her improvement continued, so that when discharged from the hospital, her physical examination was entirely negative and she appeared clinically well. She was found to be in good health at a follow-up examination 6 months later.

Case 3. This 37 year old white male veteran was admitted to Valley Forge General Hospital on 2 May, 1949, in hepatic coma. He had enlisted in the Army in July, 1942, spent 1 year in the states, then 2 years in the South Pacific theater. He had no history of jaundice nor any other serious diseases during his military service. He was discharged in early 1946, remained well until late 1946 when he developed deep jaundice lasting approximately 3½ months. He had pruritus, but not much abdominal pain or fever. He developed massive subcutaneous hemorrhages, and for several days was irrational but not comatose. He had extreme anorexia and lost considerable weight. He was treated at home by his family physician throughout this illness. After about 5 months following the onset of jaundice he had improved to the point where he could take a job as a mail clerk. He had to quit work, however, in December, 1948, because of fatigue and "weak legs". For the first 4 months of 1949 he remained at home and led a sedentary life. Approximately 1 month prior to this hospitalization he felt worse than usual and remarked that he thought his jaundice was coming back. Visible jaundice did not become obvious, however, until 2 weeks later. The intensity of his jaundice gradually increased but was not accompanied by abdominal pains or fever. He remained ambulatory at home until 4 days prior to hospitalization. His appetite was poor and he ate very little food but continued to take a drink of whisky periodically. Two days before admission he fell to the floor while trying to get out of bed and could not rise without help. One day later he became comatose and was in this state when he arrived at Valley Forge.

The patient had consumed large amounts of whisky over at least the past 10 years. He could not estimate the amount accurately, but stated that he had had some whisky at least every day.

On admission he appeared critically ill, with deep, greenish-yellow discoloration of his skin and sclerae. He was in deep coma and could not be aroused by painful stimuli. Respirations were Cheyne-Stokes in character; temperature 102°; pulse 120, and the eyelids were adherent because of a yellow exudate. There were coarse inspiratory and expiratory rales bilaterally (probably due to aspirated vomitus). Through an obese abdominal wall a large, firm liver was palpable 12 cm. below the right costal margin and 15 cm. below the xiphoid process. The spleen was not palpable on admission but was felt 7 cm. below the left costal margin 2 weeks later. Blood pressure on admission was 140/70. The genitalia revealed a very small penis and moderately small testicles, with an overabundance of pubic adipose tissue.

There was no gynecomastia. Neurological examination revealed positive Babinski signs bilaterally.

Initial blood studies were as follows: White blood count 8,300 (3% bands, 71% segmented neutrophils, 21% lymphocytes, 4% monocytes, 1% eosinophils). The hemoglobin was 9.7 gm.; red blood count 3,000,000. The BUN was 18 mg. per 100 ml., blood sugar 108 mg., serum CO_2 66 volumes %, 1 minute serum bilirubin 19.4 mg., total serum bilirubin 28.4 mg. per. 100 ml.

Initial therapy consisted of oxygen by mask, 10% glucose and later Amigen intravenously (approximately 3000 cc. daily), 2 transfusions of whole blood and thiamine chloride, 200 mg. intramuscularly daily, plus repeated tracheal aspirations and constant nursing care. In addition he received aureomycin approximately 2 gm. daily parenterally (intramuscularly and intravenously) until 5 May, 1949, at which time he was maintained on 0.5 gm. of aureomycin every 6 hours by mouth until 6 June, 1949. He received a total of 67 gm. of aureomycin.

He remained comatose until 5 May, 1949 (3 days after starting therapy), at which time he began to recognize people and to take fluids by mouth. From that time on his clinical course was one of gradual improvement although he became increasingly more jaundiced during the first 2 weeks of hospitalization. His serum bilirubin reached a peak of 46.0 mg. per 100 ml. (28.4 mg.—1 minute reaction) on 13 May, 1949. Thereafter his serum bilirubin fell gradually until 14 July, 1949, at which time it was 3.08 mg. per 100 ml. total. Other tests reflecting liver dysfunction were as follows: The thymol turbidity, which was 7.7 on admission, fell gradually to 3.7; the thymol flocculation varied between 1+ and 3+, and the cephalin-cholesterol flocculation varied between 2+ and 3+ throughout hospitalization. The total serum protein, which was initially 7.28 gm. per ml., fell in one week to 6.28 and then rose to 6.5. The serum albumin, which initially was 1.07, fell to 0.82 and subsequently rose to 1.71. The serum globulin, initially 5.21 gm., was 4.79 gm. 3 months later. The Kunkel gamma globulin ranged between 5.7 and 10.4 gm. %. The total serum cholesterol was initially 122 mg. per 100 ml., with 21% esters, and rose to 125 with 30% esters on 7 July. The prothrombin time was initially 35% of normal, gradually increasing to 55%. The 2 hour urine urobilinogen varied between 0.25 and 2.7 Ehrlich units. The Harrison spot test was originally 4+, and gradually fell to 1+. The total urine coproporphyrins were reported as 251.2 γ per 24 hours at the time of admission. His Wassermann test was negative. An examination of stools for ova and parasites was negative. The stool culture grew Pseudomonas only. Urinalyses, which initially showed 1+ albumin and 1+ sugar, subsequently were negative. A chest roentgenogram on admission revealed nothing abnormal. A flat plate of the abdomen showed enlargement of the liver and what appeared to be a slightly enlarged right kidney shadow. A gastrointestinal Roentgen-ray series on 2 June, 1949, was negative except for a diverticulum of the duodenum.

It was the opinion of the medical staff that this patient had portal cirrhosis with marked liver decompensation. This diagnosis was confirmed by a liver biopsy performed on 21 July. On 22 July BSP test showed 41.8% retention in 45 minutes. The patient recovered from acute liver failure, but continued to exhibit the findings of portal cirrhosis.

Case 4. This 60 year old white male claimed good health until 6 months prior to admission when he noted the gradual onset of weakness and progressive abdominal swelling. There had been no prior serious illness but there was known hypertension for a period of 15 to 20 years. Since the death of his wife 4 years previously, he had indulged in alcohol to considerable excess and the dietary intake, especially of late, was markedly deficient. There was no history of prior jaundice, no hemoptysis or melena, occasional vomiting and severe anorexia.

Physical examination revealed a white male with appearance of chronic illness. There was no definite disturbance in sensorium. Scleral icterus was noted. Eyes revealed grade II hypertensive retinopathy. No lymphadenopathy. In the lungs there was dullness at the left base and breath sounds were absent. There were rales in this area and at the right base. Cardiac examination was not remarkable. The blood pressure was 200/100. There was a left sided gynecomastia and several spider angiomata over anterior chest and arms. The abdomen was very markedly distended with abdominal fluid present. The liver was palpable but the exact size was not determinable because of marked abdominal swelling. It was not possible to determine palpability of the spleen for the same reason. There were a few dilated abdominal veins. The testes were not grossly remarkable. The rectum was normal on digital examination. The extremities revealed 2+ pitting edema and hyperpigmentation.

Impression on admission (August 22,

1949) was (1) diffuse hepatic fibrosis, decompensating and possibly associated with pleural effusion; (2) hypertensive cardiovascular disease.

The patient was placed on a high protein diet with low sodium (Lonalac) choline and vitamins.

Weight loss occurred almost immediately, and a week after admission, the liver was palpable 6 to 8 cm. below the right costal margin. The spleen was not palpable. By the end of 2 weeks, there had been a 30 lb. weight loss attributable to diuresis, and the patient began to demonstrate mental confusion and stupor. The possibility of electrolyte imbalance was considered. Serum electrolytes revealed serum Na 128 mEq. (moderate depression), serum K 3.8 mEq. (low normal). It was thought in conjunction with other laboratory tests that this was not primarily electrolyte disturbance and it seemed that coma secondary to hepatic failure was imminent. (CO_2 27 vols. %, BUN 24 mg. %, CL 112 mEq.)

On October 15th, he had improved sufficiently to be ambulatory. There was no appreciable change in the abdominal findings, and this state continued until the morning of October 22nd (13 days after it was noted by the Resident that his mental state was clearer than at any time since admission and 12 days after cessation of aureomycin) when he demonstrated mental confusion, stupor, and then lapsed into coma. This state continued. On October 24th, aureomycin was begun intravenously, and on October 26th, he became conscious, although the sensorium was disturbed. (See Fig. 1.) He continued to improve slowly but steadily, and on November 30, aureomycin was discontinued. By November 20th (as noted by ward staff), he seemed fairly well oriented, but the following day definite and marked evidence of disorientation was noted and he was placed on intravenous medication. This condition gradually worsened and he slipped into coma on November 24th. Aureomycin was reinstituted but the comatose state persisted until

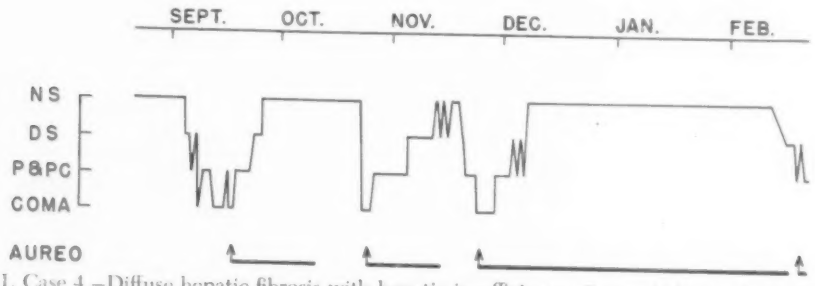

FIG. 1. Case 4.—Diffuse hepatic fibrosis with hepatic insufficiency. Course in hospital as related to aureomycin therapy 0.5 gm. every 6 hours. NS = normal sensorium; DS = disturbed sensorium; P & PC = pre and post coma; coma = hepatic coma; aureo = aureomycin, intravenous or oral.

Attempts were made to relieve the acidosis and the patient seemed to recover from his comatose state, but 2 days later (September 13, 1949) became comatose again, and on Sept. 16, 1949, was again out of coma but still revealed generalized CNS phenomena. On September 17th, the patient was once again comatose and seemed in a terminal condition.

At this time, in addition to the usual regimen, he was given aureomycin 0.5 gm. every 6 hours intravenously and later by mouth. During the following 8 days, he began to improve steadily and by October 9th, he was mentally clear, his appetite was good, his weight had dropped 30 lbs. from the admission weight. He began to be intolerant of oral aureomycin, and on October 10th aureomycin was discontinued.

November 28th when he began to respond to minor stimuli. From this time on, he continued slowly to improve until December 7th when he was definitely out of coma, answered questions rationally, and began taking food by mouth.

He improved steadily. The hospital course became complicated by 3 episodes of circulatory collapse, each following removal of considerable fluid (1500 to 2000 cc.) from the left pleural space. The last time, the fluid on culture demonstrated paracolon bacilli. Despite these episodes, he continued to improve steadily subjectively, although the physical examination of abdomen and the hepatic tests showed no significant change. A course of cortisone was begun on February 13th, 1950 (to be reported elsewhere), and on February 16th he showed some mental

aberrations and became incontinent. This state persisted with evidence of a rising BUN and creatinine. On February 20, 1950, the supply of aureomycin was exhausted, and thence discontinued. On February 22, following removal of 3000 cc. of pleural fluid, he went into peripheral circulatory collapse and died.

Autopsy Report. 1, *Portal Cirrhosis. Gross Description.* Liver weight, 1280 gm. The surface was marred by irregularly placed nodules of pale tan tissue varying in size from 0.2 to 0.6 cm. The capsule was not thickened. The parenchyma was very hard. On section numerous small nodules projected from the surface. Some of these appeared yellow or orange in color. Between them were thin bands of grey tissue. None of the usual landmarks were recognizable. A few vessels were prominent. *Microscopic.* Sections disclosed the parenchyma of the liver to consist of varying sized nodules of hepatic cells arranged in cords. The nodules were widely separated by bands of connective tissue composed chiefly of collagenous fibers and condensed reticular fibers. In this connective tissue, mononuclear cells were frequent, as were bile ducts. The blood vessels were for the most part thin walled and small but a few well developed arteries were present. Within the hepatic nodules several changes were observed. Some of the cells contained lipid vacuoles while others were filled by globules of golden brown pigment. Central veins were distorted in outline. Some veins, together with adjacent sinusoids, were congested. Foci of intranodular fibrosis were also seen.

2, *Other postmortem findings*: *a*, Left pleural empyema (paracolon infection). *b*, Left ventricular hypertrophy. *c*, Advanced arteriosclerosis. *d*, Atelectasis left lung; acute edema, right; emphysema. *e*, Congestive splenomegaly. *f*, Nephrosclerosis; chronic pyelonephritis. *g*, Marked testicular atrophy. *h*, Gynecomastia. *i*, Thrombosed esophageal varices.

Discussion. In cases of "acute yellow atrophy" or acute hepatic necrosis, usually secondary to viral hepatitis, it is well recognized that the more severe degree of necrosis occurs in the left lobe of the liver. The blood in the portal vein which reaches the left lobe drains to a great extent the large bowel, as well as the spleen and stomach, while that which reaches the right lobe drains primarily the small intestine. The difference between the 2 lobes in the degree of necrosis has been attributed to the difference in nutriments entering these lobes from the respective bowel segments. The work on aureomycin reported above, together with studies on rats (György, Stokes, Smith, and Goldblatt, Am. J. Med. Sci., **220**, 6, 1950) strongly suggest that the division of nutriments between the 2 liver lobes may not entirely account for the difference in the degree of necrosis, but that absorption of bacteria, bacterial products, or materials formed by bacterial action on bowel contents may be a far more important factor. Bacterial action and numbers of bacteria are far greater in the lower bowel than in the upper, and thus blood draining the lower bowel and going to the left lobe may carry with it sufficient organisms or products of organisms to increase differentially the degree of necrosis in this lobe.

The apparent response to aureomycin here recorded appeared to be sufficiently striking in the first 2 cases and in the 4th case to suggest strongly an improvement resulting from the activity of this drug. In Case 4 the cessation of coma appeared to be clearly related on 3 successive occasions to the administration of aureomycin. This action could have occurred in the intestinal tract or by antibacterial action within the liver itself, or possibly within the circulatory system. It is also possible that aureomycin may have had some direct action on the liver itself.

The possibility of favorable action by aureomycin is further supported by the fact reported in Part IV, namely, that in a number of cases of chronic liver disease, when aureomycin therapy was stopped, the liver disease immediately increased in severity,

as indicated by the clinical picture and by a number of liver function tests.

Summary. Four cases of acute hepatic coma—2 secondary to acute viral hepatitis, and 2 to portal cirrhosis—were treated both parenterally and orally with aureomycin. All improved shortly after such therapy was started. In 3 cases the improvement was sufficiently striking to suggest that aureomycin may well have been responsible for the change. In Case 4 it is difficult to attribute the improvement to any therapy other than the parenteral aureomycin.

STUDIES ON THE USE OF AUREOMYCIN IN HEPATIC DISEASE*
IV. AUREOMYCIN THERAPY IN CHRONIC LIVER DISEASE**
With a Note on Dermal Sensitivity

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Thirteen patients with chronic liver disease were used in this study. There was one 17 year old white female; the rest were male patients (11 white and 1 negro), ranging in age from 15 to 58 years. This group of patients had been under observation from 4 to 15 months. Eleven were studied at the Army Hepatic and Metabolic Center and 2 (Cases 2 and 6) were under the care of one of the authors (J. R. N.). Nine of the cases gave a history of what appeared to be acute viral hepatitis with jaundice at some time prior to the present hospitalization. One (Case 7) had no clear-cut history of hepatitis or jaundice but was known to have had a maximal exposure to viral hepatitis in Italy during World War II. Two cases had portal cirrhosis, etiology undetermined, but probably on an alcoholic and, or, nutritional basis. One (Case 6) with hepato-splenomegaly, abnormal liver function tests, and cellular infiltration and increased fibrous tissue on liver biopsy was difficult to classify from the standpoint of etiology. The patients selected for this study were those who appeared to be relatively stable after a suitable period of observation on the usual therapeutic measures employed in chronic liver disease, *i.e.*, bedrest, nutritious diet, and vitamin supplements. The attempt was made to continue the same general management during and after aureomycin therapy as had been employed during the observation period prior to instituting aureomycin treatment.

Methods and Materials. The diagnosis of chronic liver disease in this group had been made on the basis of history, physical findings, and laboratory studies of hepatic function. In all cases a needle biopsy of the liver was obtained before aureomycin therapy was started. A battery of liver function studies was performed in all cases of frequent intervals before, during and after aureomycin treatment. These studies included the 1 minute and total serum bilirubin determination, thymol turbidity and thymol flocculation tests, cephalin-cholesterol flocculation test, Kunkel gamma globulin determination, Harrison spot

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test and 2 hour urine urobilinogen determination. When indicated the 5 mg. per kg., 45 minute bromsulfalein dye retention test was used to follow the progress of the patients. Other laboratory studies included the determination of alkaline phosphatase, prothrombin time, serum albumin and globulin, total cholesterol and cholesterol esters. Twenty-four hour urine urobilinogen determinations were obtained when indicated. During and for a suitable period after aureomycin therapy, complete blood counts, routine urinalyses, prothrombin times, and bleeding and clotting times were obtained at weekly intervals in the 11 cases followed at the Army Hepatic and Metabolic Center.

Aureomycin was administered orally in 250 mg. capsules. The usual dosage schedule was 2 gm. a day (0.5 gm. every 6 hours) for 30 days. One patient received 2 courses of aureomycin consisting of 40 gm. in 13 days and followed after an interval of about 2 weeks by 60 gm. in 30 days. Two cases have received a total of 120 gm. in 60 days. In 1 (Case 2) the dosage varied from 0.75 gm. to 1.5 gm. a day for 66 days. One (Case 6) received 2 gm. a day for 60 days and has now been continued on a dose of 1 gm. a day for 40 days.

With the exception of the 2 cases which have just completed a 60 day course of aureomycin, and the 1 case still on 1 gm. a day, all of the patients in this group have been observed for 1 to 4 months after discontinuing the drug. (Four other cases of chronic liver disease now receiving aureomycin are not included in this report.)

Toxic Reactions to Aureomycin. In only one case, the 17 year old female, did therapy have to be discontinued because of the development of severe nausea and anorexia. Mild to moderate gastric distress was not unusual in most of the other cases, but was fairly well relieved by aluminum hydroxide gel or small feedings given with the aureomycin. Burning and itching about the rectum occurred in a few cases. Most patients had frequent loose bowel movements during the first few days of aureomycin treatment and a few patients developed frank diarrhea. The female patient developed a diffuse petechial rash of the forearm extending from the elbow to the wrist following the application of a tourniquet for collection of a blood specimen. This phenomenon occurred at the completion of her first 66 day course of aureomycin.

In none of the 11 cases observed at the Army Hepatic and Metabolic Center were any significant changes in the urine, blood counts, bleeding and clotting times or prothrombin times observed during or after aureomycin therapy.

Dermal Sensitivity to Aureomycin. In 5 cases skin changes were observed which appeared to be related to aureomycin therapy. Of interest is the fact that in 4 of these patients exposure to sunlight seemed to be an initiating factor in the development of the skin changes. This fact suggests that aureomycin may be a photosensitizing drug. In 3 of the 5 cases nail changes were associated with the skin lesions. Case 4 developed what appeared to be an unusually severe sunburn on the dorsum of both hands after exposure to sunlight on the 10th day of aureomycin therapy. The skin lesions consisted of erythema and induration with papulovesicular lesions which gradually dried and were followed by peeling of the skin of the involved areas. On the 25th day of aureomycin treatment this patient complained of numbness of both thumbs, followed by discoloration of the thumbnails with loosening from the nail beds, and hemorrhage into one nail bed. Since discontinuing aureomycin these nail changes have gradually improved. Harris[1] has reported a similar observation in one female patient as well as a solar dermatitis in 2 male patients. Case R. H., a 27 year old white male, developed skin lesions similar to Case 4 on the 15th day of aureomycin therapy, and again after exposure to sunlight. About 2 days later he noted soreness and tenderness of both thumbs. He subsequently developed slight separation of the in

volved nails from the nail bed but no nail bed hemorrhage was observed. The skin lesions in this case gradually improved with local symptomatic treatment and this patient went on to complete a 60 day course of therapy with no further skin or nail changes. Case R. M., a 35 year old white male, developed a severe erythematous, indurated, sharply marginated eruption of the dorsum of the hands and fingers with papulo-vesicular lesions on the 8th day of aureomycin treatment. The left side of the face and nose were less severely involved. These lesions developed after an automobile trip during which the hands and face were exposed to sun and wind. These lesions gradually subsided with local therapy but recurred with severe pruritus on the 27th day of aureomycin therapy. This recurrence was not related to exposure to sunlight. After stopping aureomycin the recurrence gradually subsided. Two fingernails in this case showed very slight separation from the nail bed. A skin biopsy from the involved area in this case was interpreted as showing a diffuse subacute dermatitis. Case 6 while on aureomycin was observed to be definitely sensitive to sunlight and burned severely with little exposure. In previous years he had always tanned rapidly and had not burned as he did while receiving aureomycin. Case S. T., a 42 year old negro male, developed pruritus of the feet and legs on the 2nd day of aureomycin treatment followed by the onset of pruritic papulo-vesicular lesions on the hands, fingers, forearms, legs, and on the ears. There was no unusual exposure to sunlight in this case. The patient stated that there was an exacerbation of the pruritus with new crops of lesions about 1½ hours after each dose of aureomycin. The administration of an antihistaminic drug afforded considerable relief from the pruritus and the skin lesions receded in size but were still visible. The antihistamine was discontinued at the completion of the course of aureomycin, and 24 hours later the skin lesions recurred, again with marked pruritus. This recurrence gradually subsided in about 1 week.

Limited attempts to reproduce the type of skin changes seen in the cases described above by exposure to ultra-violet light or sunlight have so far been unsuccessful. In these studies patients receiving aureomycin with no evidence of skin changes were first used. Small areas on the extremities were exposed to graduated doses of ultra-violet light with no unusual reactions. Case R. H. while still on aureomycin was similarly exposed to ultra-violet light with no unusual reaction. Case R. M. was exposed to ultra-violet light after the aureomycin had been discontinued and showed no unusual reaction.

Case Reports. CASE 1. E. S., a 22 year old white male with first episode of hepatitis with jaundice in November, 1947. The patient made an apparently normal recovery and was well until July, 1948, when he again developed jaundice, anorexia and malaise. Jaundice did not subside and patient was transferred to Valley Forge General Hospital from overseas in October, 1948. Physical findings at that time were essentially negative except for an acneform eruption of the abdomen, back and shoulders and obvious jaundice of the skin and sclerae. The liver was not palpable or tender. Blood counts were normal except for a slight anemia. The 1 minute serum bilirubin was 2.5 mg. per 100 ml. and the total serum bilirubin 4.6 mg. %. The cephalin-cholesterol and thymol flocculation tests were strongly positive and the thymol turbidity elevated to 9 to 12 units (normal 3.0 or less). The total cholesterol was 192 mg. per 100 ml. with 51% esters. Prothrombin times ranged from 50 to 65% of normal. The total serum proteins were elevated with a serum globulin of about 7.5 gm. % and the serum albumin about 3.0 gm. %. The urine was positive for bile. This patient's course has been charted in Fig. 1. This patient was asymptomatic, afebrile, eating well

and maintaining his normal average weight. A liver biopsy in January, 1949, showed marked distortion of the liver architecture with fibrous tissue, inflammatory cells and proliferating bile ducts. The diagnosis was chronic hepatitis with marked cirrhosis. This patient had been on strict bedrest, with a high caloric, high protein diet with vitamin supplements for over 3 months at this hospital with no striking change. On 7 February, 1949, he was started on the first of 2 courses of oral aureomycin. He was started on 4 gm. a day, but developed nausea and anorexia which subsided when the dosage was reduced to 2 gm. a day. The first course of 40 gm. was completed on 20 February, 1949. A 2d course of oral aureomycin was begun on 10 March, 1949, with 2 gm. a day administered for 30 days. Intravenous glucose was started between courses of aureomycin, and given 5 days a week during and for a short time following the second course of aureomycin. During this time he also received intravenous concentrated human albumin, 50 gm. a week. As can be seen from Fig. 1, this patient has shown a definite gradual improvement since the institution of the aureomycin, glucose, albumin therapy. The serum bilirubin determinations have been within normal limits for 3 months. The flocculation tests have gradually returned toward normal, as has the thymol turbidity. The urine has been consistently negative for bile. Bromsulfalein dye retention tests have been performed at intervals since the jaundice disappeared and have shown a progressive decrease from 16.2 to 7.6% retention in 45 minutes. This patient was gradually ambulated after his jaundice disappeared and he has been on normal activity for 2 months. Of interest is the fact that the patient's liver has become palpable and now extends from 5 to 7 cm. below the right costal margin on deep inspiration. Two needle biopsies of the liver have been obtained subsequent to completion of therapy. One was obtained 18 days after completing aureomycin and the second 4 months after completion of treatment. These biopsies showed an increase in the amount of relatively normal liver tissue. However, scattered throughout these areas were increased numbers of fibroblasts and areas of round cell infiltration. There were also still large areas of fibrous tissue with bile duct proliferation.

Case 2. J. T., a 17 year old white female who developed anorexia with no other unusual symptoms in January, 1948. Six months later it was observed by others that her skin and sclerae were jaundiced. The jaundice persisted despite a month of bedrest. The patient

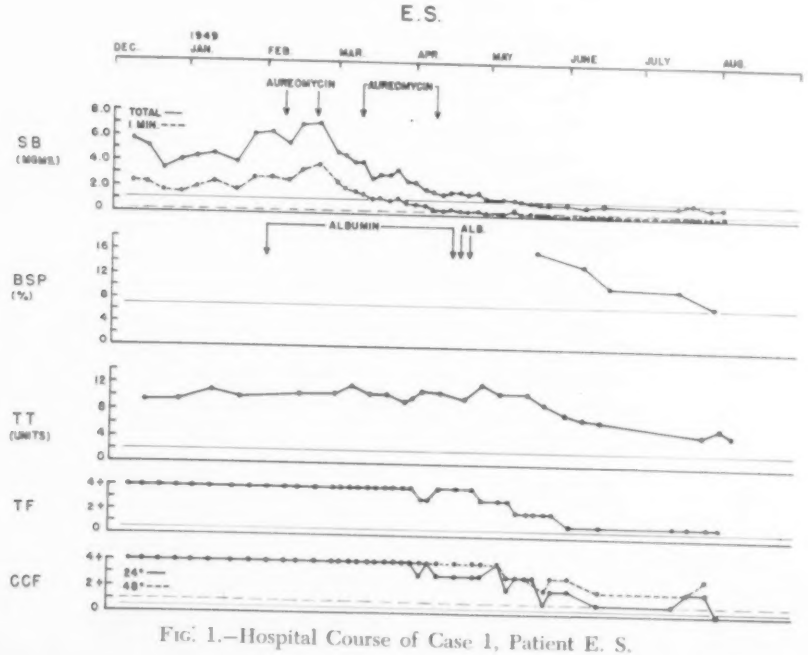

Fig. 1.—Hospital Course of Case 1, Patient E. S.

was seen by one of us (J. R. N.) in February, 1949, at which time she had been jaundiced for 8 months. The only symptoms during this time were intermittent nausea and pronounced weakness. Physical examination revealed a jaundiced white female with moderately severe facial and neck acne. There were venous blue angiomata on the forehead, at the left border of the nose, and in front of the left ear. The liver was palpable laterally and had a rounded, firm, non-tender lower border. The tip of the spleen was just palpable. Laboratory studies showed a normal white blood count and differential. The hemoglobin was 12 gm. Urinalysis was negative except for a trace of albumin and was positive for bile. Liver function studies showed a 1 minute serum bilirubin of 4.1 mg. and a total serum bilirubin of 7.2 mg. The cephalin-cholesterol and thymol flocculation tests were strongly positive. The thymol turbidity was 8.0 units and the alkaline phosphatase 10.5 Shinowara units. The total cholesterol was 169 mg. per 100 ml. with 50% cholesterol esters. Prothrombin time was 57% of normal. The serum albumin was 2.8 gm. % and the globulin 5.8 gm. %. Cholecystograms failed to visualize the gallbladder. Needle biopsy of the liver on 15 March, 1949, was interpreted as showing chronic active hepatitis with early diffuse hepatic fibrosis and post-necrotic scarring. This patient developed pruritus for the first time on 8 March, 1949. The first course of aureomycin was started on 21 March, 1949, with a dosage of 250 mg. every 4 hours. The dose was reduced to 250 mg. every 6 hours after 1 week. On 3 May, 1949, the dosage was reduced to 250 mg. every 8 hours, and the first course of aureomycin was completed on 26 May, 1949, with a total dosage of 61.5 gm. in 66 days. The patient's course is charted in Fig. 2. While on aureomycin the patient's general well-being improved. Her weight increased 5 lbs. and as can be seen from Fig. 2, her jaundice decreased in intensity. However, 2 weeks after the aureomycin was discontinued she became more jaundiced and developed slight nausea,

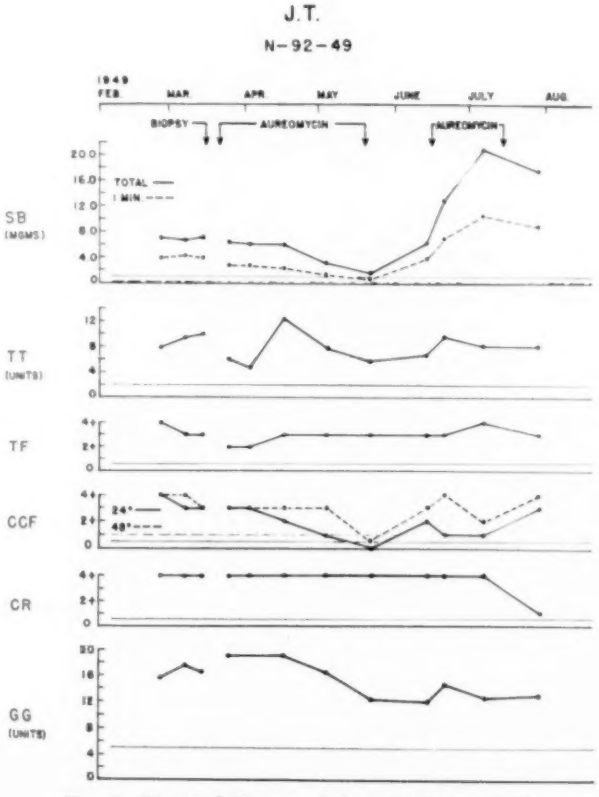

FIG. 2.—Hospital Course of Case 2, Patient J. T.

malaise, and discomfort in the back and epigastrium. The urine again became dark in color and the sclerae were again definitely icteric. Physical examination at this time revealed slight epigastric tenderness. The liver was difficult to palpate and the spleen was still palpable. A second course of aureomycin was started, but had to be discontinued because of the development of nausea and anorexia. As can be seen from Fig. 2, this patient had a definite relapse after the first course of aureomycin was discontinued. Thereafter the course was progressively downhill and the patient subsequently died from massive hepatic necrosis about 5 months after the onset of the relapse.

Case 3. J. D., a 31 year old white male with first episode of hepatitis with jaundice in January, 1947. He made an apparently uneventful recovery and was well until July, 1947, when he again developed dark urine, anorexia and jaundice. The jaundice again subsided on bedrest and the usual hepatitis regime, but he continued to have an abnormal bromsulfalein retention of from 8 to 12% in 45 minutes. After 4 months' hospitalization, he was returned to duty and felt well until July, 1948, when he again developed jaundice with an enlarged, tender liver. The jaundice again rapidly subsided, but he continued to have an elevated BSP retention as well as a positive thymol flocculation test and an elevated thymol turbidity. BSP tests at intervals from August to December, 1948, showed from 9 to 20% retention in 45 minutes. Despite all advice this patient consumed moderate amounts of alcohol throughout his illness. He was returned to the United States from overseas in December, 1948, and was admitted to this hospital 1 January, 1949. At that time he felt well. Physical examination at this time was negative except for injected sclerae and a few small spider naevi on the back. The liver and spleen were not palpable. Laboratory studies showed a normal white blood count and differential. The hemoglobin was 13.2 gm. Urinalysis was negative. Liver function tests showed a normal 1 minute and total serum bilirubin. The thymol turbidity was slightly elevated to 4.4 units and the thymol flocculation test was 0 to 1+. The cephalin-cholesterol flocculation test was negative. The urine was negative for bile. The alkaline phosphatase was 8 King-Armstrong units and the BSP test showed 15% retention in 45 minutes. The total cholesterol was 250 mg. per 100 ml. with 71% esters. The total serum proteins were 7.36 gm. % with an albumin of 4.46 gm. % and a globulin of 2.90 gm. %. Needle biopsy of the liver on 24 February, 1949, showed chronic active hepatitis with moderate cirrhosis and fatty infiltration. During a period of 2½ months on an ambulatory status, with a high caloric, high protein diet there was no change in the liver function studies except that the BSP retention increased to 17.5% and then 27% on 15 March, 1949. The patient was started on a 30 day, 60 gm. course of aureomycin on 21 March, 1949. His only reaction to the drug was an intermittent diarrhea. During aureomycin therapy the BSP retention gradually decreased to a low of 4.3% 9 days after completing the course of therapy. The thymol turbidity test also dropped to within normal limits. Complicating the evaluation of this case is the fact that this patient reduced his alcohol consumption for a period preceding and during aureomycin therapy. He was observed for 3 months following aureomycin treatment and during this time he had a 1 week episode of moderate to heavy alcohol intake. Subsequently, his BSP retention increased to a peak of 33.5% and then gradually decreased to 8.7% after he again adhered more closely to the recommendation to abstain from alcohol. A needle biopsy of the liver performed at the completion of the 30 day course of aureomycin was interpreted as showing no significant improvement in the pathological picture.

Case 4. H. M., a 32 year old white male who had the onset of anorexia, nausea, chills and fever, dark urine and jaundice in August, 1948. He made an uneventful recovery on routine management until about 12 October, 1948, when his jaundice, which had been clearing, became deeper and the total serum bilirubin increased from 2 to 4 mg. He was returned to the United States from overseas in November, 1948, and arrived at this hospital on 27 December, 1948. He was asymptomatic and afebrile at that time. Physical examination was not remarkable except for slightly icteric sclerae. The liver was not palpable or tender. Laboratory studies were within normal limits except for the liver function tests which showed a normal 1 minute serum bilirubin but a persistently elevated total serum bilirubin of from 1.2 to 2.0 mg. per 100 ml. The thymol turbidity ranged from 3.2 to 5.9 units and the thymol flocculation test from 2+ to 3+. The cephalin-cholesterol flocculation test was slightly positive. The urine was negative for bile. The BSP test showed from 4 to 5% retention in 45 minutes. The prothrombin time ranged from 86 to 100% of normal. The tot

cholesterol was 330 mg. per 100 ml. with 69% esters. The total serum protein was 7.63 gm. % with the albumin 3.89 gm. % and the globulin 3.74 gm. %. On bedrest the thymol turbidity returned to normal and the flocculation tests became negative. However, the total serum bilirubin continued to be slightly elevated. A needle biopsy of the liver was obtained on 8 March, 1949, and was interpreted as showing no significant abnormalities. This patient was started on a 30 day, 60 gm. course of aureomycin on 26 April, 1949. After 1 week the course of treatment was interrupted when the patient was absent without leave for 6 days. The treatment was then completed without further interruption or complication except for skin and nail changes described in more detail in the section on dermal sensitivity to aureomycin. No significant change in the total serum bilirubin level was noted until the completion of the course of aureomycin when a value of 0.86 mg. was reported. Three subsequent determinations in the following week ranged up to 1.02 mg. These determinations of the total serum bilirubin were the only normal values reported in the 6 months this patient had been under observation here. However, 1 month later the total serum bilirubin was again 2.0 to 2.5 mg. and was still in this range 2 months after completing aureomycin therapy when he was lost from observation.

Case 5. S. C., a 49 year old white male who developed hepatitis with jaundice in 1942 after receiving yellow fever vaccine. He was ambulated at that time before his jaundice had disappeared and continued to have symptoms of fatigue, malaise and lethargy which slowly subsided after several months. In the intervening 7 years he had no known recurrence of jaundice. During this time he did have intolerance to fatty foods, and frequent bloating after meals. In the 6 months before he was seen at this hospital his gastrointestinal symptoms had become somewhat more severe and accompanied by slight anorexia. He had never been a heavy drinker and had abstained from alcohol completely for 6 months after his hepatitis and since then had been only a social drinker. Physical examination was negative except for injected sclerae. The liver and spleen were not palpable. Roentgen-ray examinations of the gastrointestinal tract and gallbladder revealed no abnormalities. Stool examinations were negative for ova and parasites. Blood counts and hemoglobin were normal and urinalysis was negative. Liver function studies were all within normal limits except for the BSP test which showed 17.2 and 18.9% retention in 45 minutes on 2 determinations. Needle biopsy of the liver obtain 12 April, 1949, showed moderate to severe fatty metamorphosis. The patient was on an ambulatory status during hospitalization. He was started on a 30 day, 60 gm. course of aureomycin on 3 May, 1949. The only side effects to the drug noted in this case were moderate gastric distress, a short period of diarrhea, and itching and burning of the rectum. BSP tests done at 2 week intervals during the course of aureomycin showed 16.2%, 20.0% and 22.5% retention in 45 minutes. The first drop in BSP retention was not observed until almost 2 months after the aureomycin therapy was completed, when the test showed 7.1% dye retention in 45 minutes. A needle biopsy of the liver performed 2 months after the completion of the course of aureomycin showed no improvement in the histological picture. Subsequent follow-up in this case has shown a gradual rise in the BSP retention. Two and one-half months after the completion of aureomycin treatment the BSP retention was again 19% in 45 minutes. Subjectively the patient improved with an increase in strength and energy, and with fewer gastric symptoms.

Case 6. D. W., a 15 year old white male referred to one of us (J. R. N.) in April, 1949, because of bleeding gums and hepatomegaly. In 1947 the patient had recurrent attacks of abdominal pain which disappeared after eggs were eliminated from the diet. In the fall of 1948 bleeding of the gums was first noted which was mild at first but became worse in January, 1949. There was no other site of bleeding. Physical examination revealed a dry skin, with moderate acne and a few slightly raised reddish papules on the soles of the feet. There was a questionable slight scleral icterus. The gums were spongy, hypertrophied and bled easily with slight trauma. Moderate gynecomastia was present. The liver edge descended 3½ cms. below the right costal margin, was fairly firm and nontender. The spleen was palpable 4 cm. below the left costal margin. Laboratory studies showed a white blood count of 8300 with a differential count of 59 neutrophils, 26 lymphocytes, 11 monocytes, and 4 eosinophils. The platelet count was 180,000 and the hemoglobin 75% with a red blood count of 4,100,000. Urinalysis and serology were negative. Hepatic tests showed a 1 minute serum bilirubin of 0.38 mg. with a total serum bilirubin of 1.08. The thymol turbidity was 6.4 with a 3+ thymol flocculation. The cephalin-

cholesterol flocculation test was 3+ in 24 hours. BSP retention was 24.7% in 45 minutes. The serum albumin was 3.9 gm. with the globulin 4.3 gm. The alkaline phosphatase was 13.5 Shinowara units and the prothrombin time 66% of normal. The total cholesterol was 125 mg. per 100 ml. with the cholesterol esters 48%. Cholecystogram showed an abnormally functioning gallbladder which visualized faintly and which became slightly smaller after a fatty meal. Bone marrow examination showed a very cellular marrow with a moderate normoblastic hyperplasia with some evidence of delay in maturation. The megakaryocytes were numerous and probably increased above normal. A needle biopsy of the liver on 9 May, 1949, showed moderate vacuolization of the liver cells with a moderate number of fine to medium sized fat globules. The periportal spaces were much enlarged due to cellular fibrosis. There was also considerable infiltration with lymphoid cells and some eosinophils. In addition there was an increase in the small bile ducts. The patient was started on aureomycin 2 gm. a day on 16 May, 1949. On 21 May the drug was discontinued for 48 hours because of mild gastrointestinal symptoms but was then resumed. While on aureomycin this patient was observed to be sentitive to sunlight and burned severely with little exposure. The aureomycin was reduced to 1 gm. a day on 18 July and has been maintained at this dosage for 40 days at the time this report was prepared.

During aureomycin therapy this patient's general condition improved and his skin lesions cleared. The liver and spleen decreased in size but remained palpable. Hepatic function tests have shown a slow, gradual trend toward normal. The serum bilirubin has dropped to within normal limits. The colloidal red test has gone from 4+ to 1+ and the BSP retention decreased slightly to 22% in 45 minutes. The cholesterol esters gradually increased from 43% in April to 70% in August, 1949. The general over-all impression in this case has been one of definite improvement. At present it is planned to maintain this patient on aureomycin for an indefinite period.

Case 7. N. P., a 37 year old white male with no clear-cut history of liver disease prior to 1948. While in the Army in 1944 he was quartered in Italy with a group of 12 men, of whom about 50% developed acute viral hepatitis with jaundice. The patient was well until June, 1948, when he developed pain in the epigastrium and right upper quadrant. No jaundice or dark urine was observed. In October, 1948, at another hospital, liver function tests showed borderline abnormalities with a BSP retention of 6%, increased 24 hour urine urobilinogen and slightly positive flocculation tests. Subsequent follow-up studies showed a progressive development of abnormal hepatic function manifested mainly by BSP retention which gradually increased to 17% in June, 1949, prior to admission to this hospital. A needle biopsy of the liver in February, 1949, showed cellular infiltration, some destruction of liver cells, and an increase in fibrous tissue. A second biopsy in May, 1949, showed progression of the liver disease with considerable destruction of liver cells adjacent to areas of fibrosis. The lobules were greatly altered in comparison to the first biopsy. A diagnosis of chronic hepatitis and early cirrhosis was made. This patient was placed on bedrest and started on a 30 day course of aureomycin on 7 June, 1949. At that time he was essentially asymptomatic and the only positive physical findings were a palpable liver 4 cm. below the right costal margin which was slightly tender. The spleen was just palpable below the left costal margin, and there were a few small spider naevi on the arms and shoulders. Laboratory studies showed a normal white blood count and differential with a hemoglobin of 10.4 gm. Liver function tests showed slightly positive flocculation tests and a BSP retention of 23.6% in 45 minutes. The serum bilirubin was normal. The patient tolerated aureomycin well with no significant side effects. At the completion of the course of aureomycin the BSP test had decreased to 9.6% retention. One month after completing aureomycin therapy the BSP retention was 2.9% in 45 minutes. During the therapeutic regime of bedrest and aureomycin the patient gained 10 pounds in weight and he stated that he had less fatigue and fewer symptoms.

Of the 6 cases that failed to show any appreciable improvement that could be attributed to aureomycin therapy, 2 had moderate to severe portal cirrhosis, and 4 had chronic hepatitis apparently initiated by episodes of acute viral hepatitis. In this group were 3 cases that manifested reactions to aureomycin that are described in the section on dermal sensitivity.

Discussion. Well controlled evaluation of therapy in chronic liver disease is difficult to achieve. In this study

each patient served as his own control during a period of observation on a basic regimen prior to institution of aureomycin therapy. The possible delayed effects of such a general therapeutic regimen are impossible to predict and may be manifested during or after a period of specific therapy such as aureomycin. It is felt, however, that the results of this study have revealed improvement in some of the cases reported, which appeared to be related to aureomycin therapy.

Of the 13 cases treated, it is believed that the 7 reported in detail have shown improvement that may be related to aureomycin therapy. The remaining 6 cases showed little or nothing that could be attributed to possible aureomycin effect.

Evaluation of Case 1 is complicated by the fact that in addition to aureomycin, he also received intravenous concentrated human albumin and glucose. That these therapeutic agents contributed toward the improvement noted is entirely possible. Similar cases treated with aureomycin alone are necessary to decide this point. Case 2 was similar to Case 1 but received only aureomycin in addition to general supportive therapy. There are 2 features of particular interest in this case: 1, the decrease in the serum bilirubin and striking clinical improvement while on aureomycin, and 2, the clear-cut relapse which occurred shortly after aureomycin was stopped. This case demonstrates, in addition to an apparent beneficial effect from aureomycin, that the optimal dosage and duration of treatment has not been determined. In Case 7 the progressive drop in the BSP (bromsulfalein) retention to within normal limits occurred following a period of bedrest during which time the patient received aureomycin. The improvement in this case may therefore have been due to the bedrest rather than to the aureomycin. However, cases 3 and 5 provide at least suggestive evidence that a reduction in BSP retention may be brought about by aureomycin therapy. Both of these patients were on an ambulatory status while receiving aureomycin and in both cases a temporary drop to normal or near normal levels resulted. Evaluation of Case 3 is difficult because of the variable alcoholic intake before, during, and after aureomycin therapy. In Case 5 the delayed, short-lasting drop in BSP retention cannot be explained on the basis of variable alcohol consumption or a change in any other factor of the basic regimen that we can detect. All that can be said in this case is that the BSP retention which had ranged from 16.2 to 22.5% for almost 3 months, dropped to 7.1% about 2 months after a course of aureomycin was completed. This drop toward normal was only temporary and within 3 weeks had returned to the pre-therapy level. In Case 4 the drop in the total serum bilirubin to normal limits occurred at the completion of aureomycin therapy and was again of only short duration. It seems at least suggestive of aureomycin effect in this patient that 4 serum bilirubin determinations during a period of 1 week after completing therapy ranged from 0.86 to 1.02 mg., whereas repeated determinations in the previous 5 months had all been slightly elevated above normal. Of added significance is the rise to the pre-treatment level within 2 weeks after aureomycin was discontinued. This apparent escape as a result of stopping therapy we believe is an important criterion of the value of treatment in any chronic disease. It is unfortunate that it has not been possible to give this patient a second course of aureomycin in an attempt to duplicate these suggestive results. In Case 6 there has been a gradual,

definite improvement in the patient's clinical condition as well as improved hepatic function as reflected by liver function tests. This patient is the only one of the group still receiving aureomycin and final evaluation of this case must be deferred.

The results of this study suggest that aureomycin therapy may be beneficial in some types of chronic liver disease. The evidence to date is largely suggestive and only further study can determine the validity of the impressions obtained from the group of patients reported here.

The mechanism of action of aureomycin in liver disease is not known. At the present time there is no proof that aureomycin is effective against the hepatitis virus, or that the virus is even present in cases of chronic hepatitis which appear to follow an original acute viral hepatitis. The answer to such questions will await the development of experimental tools which may be used to study these problems.

An interesting side-effect of aureomycin was observed in this study. This side-effect consisted of skin and nail changes in 4 patients which apparently developed after exposure to sunlight. These reactions suggest that aureomycin may be a photosensitizing agent, in at least some cases. This possibility must be kept in mind in the care of patients receiving aureomycin. Our observations have been limited to patients with chronic liver disease and we cannot say at this time whether or not hepatic dysfunction is an essential part of the observed reactions to aureomycin.

Summary and Conclusions. 1. Thirteen cases of chronic liver disease have been treated with oral aureomycin.

2. The usual course of therapy was 2 gm. a day for 30 days.

3. In 7 cases improvement resulted which may have been related to aureomycin therapy. Case reports of these 7 patients are presented.

4. In 6 cases there was little or no evidence of benefit from aureomycin.

5. Dermal sensitivity, manifested by skin and nail changes, was observed in 5 cases. In 4 of these 5, the lesions appeared after exposure to sunlight, indicating the possibility that under some circumstances aureomycin may be a photosensitizing agent.

6. The results of this study suggest that aureomycin therapy may be of value in some types of chronic liver disease.

Addendum: Since this report was submitted for publication, Rumball, Marion, and Sanders (Gastroenterology, **14**, 432, 1950) have reported 1 case of chronic post-hepatitis cirrhosis, with jaundice of 4 years' duration, that showed improvement, subjectively and objectively, following the institution of aureomycin therapy.

REFERENCE

1. **Harris, H. J.:** J. Am. Med. Assn., **142**, 161, 1950.

DILATATION OF THE BILE DUCTS AND INTRAHEPATIC LESIONS WITH OBSTRUCTIVE JAUNDICE IN RATS FED DIETS DEFICIENT IN VITAMIN A

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Many reports have been published on the changes which are found in the organs and tissues of animals that have been fed diets deficient in vitamin A. Since these reports have been reviewed and summarized by Wolbach and Howe[23,24], Tyson and Smith[20], Robertson[16], Wolbach[21], Bessey and Wolbach[1], Wolbach and Bessey[22], Bicknell and Prescott[2], Hart[7], and others, a further review will not be presented here. They point out that metaplasia of epithelial tissues is the most characteristic change of vitamin A deficiency. The epithelial changes that take place in the rat with vitamin A deficiency have been carefully and extensively studied and have been found to occur in the salivary glands, respiratory tract, genito-urinary tract, eye and paraocular glands, stomach and other organs of that species. However, investigators of vitamin A deficiency of that species either state that the liver and bile ducts remain unchanged or they do not include these structures in the lists of organs which do undergo pathologic change in the presence of this deficiency. It, therefore, is generally thought that changes of the bile ducts and liver do not occur in vitamin A deficiency of the rat.

Though published reports indicate that the liver and the bile ducts do not undergo changes in vitamin A deficiency, a few articles have reported the occurrence of biliary calculi in animals fed diets supplemented with cholesterol but deficient in vitamins. Stepp and Kühnau[19], without giving specific reference to their source of information, stated that concretions have been produced in the bile passages of animals on diets deficient in vitamin A. Okey[15] found calculi of calcium phosphate and cholesterol in guinea pigs fed a cholesterol-supplemented diet and suggested that for the animals of the experiment some relation of the level of vitamin B intake to calculus formation may have existed. Emiliani and Bazzocchi[3] noted a very high incidence of gallstones in guinea pigs, with or without hypercholesterolemia, in vitamin A deficiency. However, they found a low incidence of calculi in guinea pigs fed a cholesterol-supplemented, vitamin B deficient diet, and no calculi in animals fed a vitamin B deficient diet not supplemented with cholesterol. Fujimaki[4] described the formation of cholesterol calculi in rats fed a vitamin A deficient diet to which cholesterol had not been added, but failed to find biliary calculi in rats fed a vitamin B deficient diet. Reference to the last described work was also made by Saiki[17]. Fujimaki did not describe the gross and histologic condition of the liver or bile ducts of the rats which had vitamin A deficiency and which had biliary calculi, and none of the authors has suggested that the bile

ducts are in any manner structurally altered in vitamin deficiency or contribute to the formation of the calculi.

The present report presents the results of a study of vitamin A deficiency in the rat in which a large percentage of the deficient animals were found to possess obstructed and dilated bile ducts, biliary calculi, metaplasia of the epithelial lining of the bile ducts, and pathologic changes of the portal canals and hepatic lobules.

Materials and Methods. The diet used in this study was made up of purified ingredients in the proportions employed by Mayer and Krehl[13] for some phases of their recent studies on vitamin A deficiency. The basal diet mixture was composed of the following in grams per 100 grams of diet: casein (vitamin-free), 25.0; sucrose, 65.7; cottonseed oil, 5.0; salt solution no. 2 (U.S.P.), 4.0; cystine, 0.2; and choline, 0.1. To the basal diet mixture were added the following vitamins in milligrams per kilogram of diet: alpha-tocopherol, 100; 2-methyl-1, 4-naphthoquinone, 5; D_2 (viosterol), 0.1; thiamine, 5; pyridoxine, 5; riboflavin, 5; nicotinic acid, 50; pantothenic acid, 50; inositol, 100; para-aminobenzoic acid, 100; and folic acid, 0.5. Vitamins A and C and biotin were not added to the basal diet mixture.

Forty-nine rats were prepared for study by placing the mother and young on the diet deficient in vitamins A and C when the young were 10 or 11 days of age. The young rats were weaned at 21 days of age, placed in separate cages and divided into 4 groups. The number of animals in each group and the feeding regimen for the various groups are given in Table 1. All animals were supplied with unlimited quantities of water and of the diet mixtures. The quantity of vitamin A supplied was in excess of minimal requirements as set forth in the studies by Nylund and With[14].

Two animals of Group 1, and 2 animals of Group 2 were killed for observation after they had been on the deficient diets for 17, 22, 14 and 24 days respectively, and before deficiency symptoms appeared, while the remaining 22 rats in those 2 groups were continued on their diets until symptoms of severe vitamin A deficiency appeared. Some of the vitamin-deficient animals of those groups died, but the greater number were killed after they had become moribund and it was evident that they would die within a few hours. The rats of Groups 3 and 4 were killed after all animals of Groups 1 and 2 had died or had been killed. Determinations of hemoglobin and of the volume of packed erythrocytes, erythrocyte and leukocyte counts, and blood smears for differential leukocyte counts were made on all animals killed. Careful and thorough necropsy studies were made of all animals, and tissues for histologic study were fixed in neutral formalin or Helly's fixative solution and stained with hematoxylin and eosin.

TABLE 1.—DESCRIPTION OF GROUPS

Group	*Animals*	*Diet*
1	13	Diet deficient in vitamins A and C only.
2	13	Diet deficient in vitamins A and C, to which ascorbic acid had been added in proportions of 100 mg. per 100 gm. of diet.
3	12	Diet deficient in vitamins A and C, with 13.5 I.U. of vitamin A added daily.
4	11	Diet deficient in vitamins A and C, to which ascorbic acid in proportions of 100 mg. per 100 gm. of diet and 13.5 I.U. of vitamin A were added daily.

Results. Table 2 presents data on age and growth for all groups of rats of this study. The results of the blood studies, which will be presented elsewhere, will be only briefly referred to here. Rats of Groups 3 and 4 fed diets supplemented with vitamin A, the former without and the latter with the additional supplement of vitamin C, exhibited similar rates of growth, had normal blood values and did not experi

ence symptoms of vitamin A deficiency or show abnormalities of the organs or tissues at necropsy and on microscopic study. All rats of Groups 1 and 2 fed the diets deficient in vitamin A for a sufficiently long period of time to permit deficiency to be established, whether or not the diets were supplemented with vitamin C, showed a similar inhibition of growth and loss of weight and gave hemoglobin values, erythrocyte counts, corpuscular volume percentages (hematocrit) and heterophil leukocyte counts that were elevated to a similar degree. In the animals of the latter groups symptoms of vitamin A deficiency developed to similar degrees of severity, and in many, symptoms of jaundice were exhibited.

TABLE 2.—SUMMARY OF NUMBER AND AGE OF ANIMALS, NUMBER OF DAYS ON DIET AND GROWTH DATA

		Average age, days			*Average weight, gm.*		
Group	*Animals*	*When placed on diet*	*When killed*	*Days on diet (average)*	*Initial*	*Final*	*Gain*
1	13	21	52.5	31.5	34.5	92.0	57.5
2	13	21	58.3	37.3	34.8	91.0	56.2
3	12	21	73.0	51.9	35.4	191.3	155.9
4	11	21	72.7	51.6	38.5	196.4	157.9

The symptoms of vitamin A deficiency shown by animals of Groups 1 and 2 included those usually found in the deficiency syndrome, namely, xerophthalmia, difficult and noisy breathing, unsteady gait, anorexia, some degree of cyanosis and abrupt and rapid loss of weight during the last 2 or 3 days before death. At necropsy and on histologic study, if they had been continued on the deficient diet for a sufficiently long period of time, these animals exhibited some or all of the gross and histologic pathologic features characteristic of the deficiency. Abscesses in the lungs, salivary glands, base of the tongue and the middle ear were present in the greater number of animals, and complete or partial obstruction of the trachea and bronchi was commonly present. Urinary calculi were not found in our specimens and only 2 animals had distended ureters and distended pelves of the kidney. Unlike the deficient rats observed by Mayer and Krehl[13], none of our animals had a bloated and distended gastro-intestinal tract. While the esophagus appeared normal, portions of the epithelial lining of the stomach of some animals were hyperkeratinized. In all animals with vitamin deficiency the duodenum was dilated and hyperemic, and the ileum and jejunum, chiefly the latter, were thin walled and transparent and contained a bloody, yellowish colored fluid. The symptoms and pathologic changes described above indicated the presence of a severe vitamin A deficiency in animals of Groups 1 and 2.

Symptoms of jaundice shown by the animals of Groups 1 and 2 with vitamin A deficiency were an icteric discoloration of the fur of the genito-urinary organs, some coloring of the ears and a faint to deep yellow color of the blood plasma when seen in hematocrit tubes. At necropsy, the inner surface of the skin of these animals was of a faint to deep yellow color, but the subcutaneous tissues were colored only in the rats with very severe jaundice. The color of the tendons and joint capsules varied from a faint to deep yellow.

Because of congestion of the blood vessels and the resulting dark color, the skeletal muscles showed a yellow color only in cases of extremely severe jaundice.

The above-described evidences of jaundice in the animals of Groups 1 and 2 with vitamin A deficiency were accompanied by obstruction and dilatation of the bile ducts and normal or but slightly abnormal appearances of the liver as disclosed at necropsy. Of the 26 rats of Groups 1 and 2, 19 (*i.e.*, 9 of the 13 in Group 1, and 10 of the 13 in Group 2) had enlarged common hepatic ducts. As noted previously, 2 rats of each of these groups were killed early in the feeding period before deficiency symptoms appeared and before dilatation of the bile ducts could have developed. Hence, of the 22 deficient rats which could have possessed enlarged ducts and accompanying changes of the liver, 19 (86%) did have them.

Pathologic Changes in the Bile Ducts. The common hepatic duct of the 19 jaundiced rats with vitamin A deficiency described above was dilated throughout its length from the portal fissure to the wall of the duodenum. The smallest of the dilated ducts measured approximately 3 mm. in diameter at a point just distal to the entrance of the right lobar hepatic duct, while the largest observed duct measured 8 mm. in diameter at the same level. The diameter of the common hepatic duct of normal rats, in agreement with the work of Mann, Brimhall and Foster[12], was found to measure 1 mm. or less at that level. The dilated common hepatic duct was widest at the point where it received the hepatic ducts of the right and caudate lobes of the liver (the names employed by Greene[6] to designate the various lobes of the liver of the rat are used in our report). The duct was narrower anterior to the point and toward its origin from the ducts of the middle and left lobes of the liver. Posterior to the point at which the right and caudate lobar hepatic ducts entered, the common hepatic duct was of fairly uniform diameter but narrowed abruptly at the duodenal end. The portion of the common hepatic duct which entered the wall of the duodenum was not noticeably dilated. The appearance of the enlarged bile ducts of rats of Groups 1 and 2 is shown in Fig. 1.

The wall of the anterior two thirds of moderately enlarged common hepatic ducts was thin and transparent, while the wall of the posterior third, or intrapancreatic portion, was dense and firm and usually quite opaque (Fig. 2). Greatly dilated common hepatic ducts possessed a thin and transparent wall throughout the greater part of their length as shown in Fig. 1. The bile within the ducts, readily seen through the transparent walls, was usually clear and colorless, or greenish yellow in color, or, as shown in Fig. 1, for 3 specimens it was white and cloudy in appearance. Microscopic examination showed the bile of all enlarged ducts to contain suspended masses of epithelial cells. These were most numerous in the cloudy-appearing bile. Bacteria and leukocytes were found in the bile of only a few specimens, chiefly in the cloudy-appearing fluid. Though calculi were found at all points along the common hepatic ducts, they were most frequently found in the intrapancreatic segment where, as shown in Fig. 2, they tended to fill the lumen completely. The epithelial cell masses also were most numerous in this segment of the duct, and together with the calculi undoubtedly offered considerable resistance to the flow of bile to the duodenum.

Four lobar hepatic ducts, namely, those of the right, middle, left and

caudate lobes of the liver, could readily be examined if the lobes of the liver were turned forward in the manner shown in Fig. 1. Those lobar hepatic ducts were dilated to some degree if the common hepatic duct was dilated, but of the lobar ducts, the right and caudate ducts were commonly dilated the most. All lobar ducts had thin and transparent walls, and clear and colorless or greenish yellow-colored bile. Masses of epithelial cells were present in the bile but usually no bacteria or leukocytes were found in these ducts. Calculi were commonly not found in the lobar hepatic ducts.

The most prominent pathologic feature of the wall of the obstructed and dilated common hepatic duct and lobar ducts of the rats of Groups 1 and 2 with vitamin A deficiency and jaundice was a great thickening and metaplasia of their epithelial lining. The degree of thickening and the completeness of the metaplasia were greater for the common hepatic duct than for the lobar ducts. Since the condition of the epithelium and the processes of metaplasia were the same for the 2 classes of ducts, only one description will be given and differences noted where necessary.

A small number of the dilated common hepatic ducts and all the dilated lobar ducts possessed an epithelium which was only moderately thickened and in a fairly early stage of metaplasia. The epithelium was stratified and composed of 5 to 10 layers of cells (Fig. 3). The cells of the basal layer were cuboidal to columnar in shape, while the intermediate layers were composed of cells of irregular form. None of the cells at the free surface of the epithelium were thin and squamous in shape but were irregularly spherical or flattened rectangular cells which frequently covered 1 or 2 underlying cells. Some of the cells were found to possess 2 nuclei. A peculiarity of the surface epithelial cells was their tendency to form polyp-like masses which were few in number and small in size in lobar ducts, but which frequently extended some distance into the lumen and were numerous in common hepatic ducts. The cells of the polyp-like masses were irregularly rounded in form and had a fairly distinct margin and uniformly stained cytoplasm. The proximal cells of the masses possessed deeply pyknotic nuclei while the nucleus of more distal cells was represented by chromatin masses or only the nuclear membrane. Frequent masses of epithelial cells with indistinct nuclei were free in the lumen; they undoubtedly had become detached from the epithelium. Numerous gland-like evaginations of the epithelium were present in the wall of the common hepatic duct. Such evaginations were rarely seen in the wall of the lobar ducts. The cells lining the evaginations were columnar in shape and normal in appearance except at the neck and mouth of the gland where stratification of the cells sometimes occurred. Metaplasia was, therefore, limited to the portions of the epithelium which bordered on the lumen of the ducts.

The most advanced stage of epithelial thickening and metaplasia was found in the common hepatic ducts only (Fig. 4). In those specimens the stratified epithelium was composed of many layers of cells, and the polyp-like masses were very numerous and very large. Except for the great increase in number of layers of cells, the epithelia were like those described above for early metaplasia. Though many polyp-like epithelial cell masses retained their attachment to the surface of the epithelium, many cell masses were free within the lumen of the duct. The cells lining the gland like evaginations continued to be columnar in shape and unstratified if the passage from the

gland to the lumen of the duct was open. Evaginations which lacked communication with the lumen of the duct were lined by a stratified squamous epithelium which in many cases had been transferred into epithelial, pearl-like bodies.

The subepithelial connective tissues formed a thin layer in the anterior region of the common hepatic ducts, but was fairly thick in the posterior or intrapancreatic portion of the ducts. Smooth muscle cells were disposed as scattered bundles of cells. Only very small numbers of leukocytes were found in the subepithelial tissues of the enlarged ducts.

Longitudinal histologic sections through the region of junction and contiguous segments of the common hepatic duct and duodenum showed the wall of the dilated hepatic duct to be abruptly and deeply constricted at the point where it fused with the wall of the duodenum. As described by Mann[11] for the rat and by Hendrickson[8], and Schwegler and Boyden[18], for other mammals and man, the constriction was found to be produced and maintained by a sphincter-like arrangement of the muscles of the wall of the duct and of the duodenum. The epithelium at this point in the duct was thickened and metaplastic and resembled the epithelium of the more anterior segments of the ducts described above. The connective tissue of the wall was not markedly thickened but frequently contained large numbers of heterophilic and eosinophilic leukocytes. Masses of epithelial cells and calculi were, in most instances, numerous in the lumen bordering on the constriction of the wall of the duct described above.

The longitudinal histologic sections of the region of junction of a dilated bile duct with the duodenum showed the intramural segment of the duct to be only slightly dilated or not to be dilated. The epithelium of this portion of the dilated duct was stratified and though not as thick as for the common hepatic duct proper, it was sufficiently thickened to reduce the cross sectional area of the lumen. Free masses of epithelial cells, calculi, mucus and, in some instances, bacteria and leukocytes almost completely filled the passageway of the intramural duct of some specimens.

Calculi and calculus-like bodies, as shown by dissections and histologic sections, were not present in any of the bile ducts of the rats of Groups 3 and 4 fed the diets supplemented with vitamin A. Calculi and calculus-like bodies varying in size from those barely visible to the naked eye to those measuring 2 mm. or more in diameter occurred in variable numbers in the dilated bile ducts of all rats of groups 1 and 2 with vitamin A deficiency and jaundice. The calculus-like bodies, readily seen through the walls of dilated ducts at necropsy, on microscopic examination, as noted above, were found to be composed of compactly arranged epithelial cells. True concretions, however, were present, and of these some were very hard and chalky white in color, while others were fragile and brittle, and dull rather than white in color. Though all calculi contained both acid-soluble and ether-soluble materials, all possessed a central mass composed of a variable number of epithelial cells. Crystals of inorganic salts, cholesterol, bile salts, and crystals to date not identified, were found on microscopic study of crushed samples of the calculi. Crystals of bilirubin were also found, but in such small numbers that the calculi were white or colorless.

The decrease in diameter of the lumen of the intramural duct and the presence of obstructing masses of epithelial cells and calculi in it and in the lumen of the intrapancreatic po-

tions of the common hepatic duct undoubtedly offered sufficient resistance to the flow of bile to produce some degree of biliary stasis and dilatation of the extrabiliary ducts. The greater number of rats with dilated bile ducts showed only a low grade of jaundice, and for those animals the passageway to the duodenum could not have been continuously or completely obstructed, so that some flow of bile, either of a continuous or intermittent character, must have occurred. That some bile did reach the intestine of those animals was shown by the presence of yellow-colored fluid and debris in the duodenum and jejunum.

PATHOLOGIC CHANGES IN THE LIVER. The livers of the rats which were fed diets fortified with vitamin A, namely, all rats of Groups 3 and 4, were found to be normal in size and appearance at necropsy and to possess normal histologic structure on microscopic examination. In addition, rats of Groups 1 and 2, though they had been fed diets deficient in vitamin A, had livers that were normal or only moderately abnormal in appearance. The livers of the rats of Groups 1 and 2 which did not possess enlarged bile ducts or had only slightly enlarged ducts, not only were of normal appearance but were also of normal histologic structure. The livers of the rats of Groups 1 and 2 which possessed markedly dilated bile ducts were approximately normal in size, had smooth surfaces and, owing to pronounced vascular congestion, were of a deep red color. The region immediately surrounding the hepatic fissure was almost always yellowish in color. Yellowish-colored areas, always small in size and irregular in outline, were also found in the central areas of the lobes of the liver of a small number of animals. Further, the livers of the rats which possessed greatly dilated bile ducts was found, on microscopic study, to have an altered histologic structure. The pathologic structure of these livers is described below.

Histologic sections through the portal fissure and surrounding parts of the liver of rats which possessed dilated extrahepatic ducts showed the major intrahepatic ducts to be dilated in various degrees. A direct relation between the degree of dilatation of these ducts and the degree of dilatation of the extrahepatic ducts could not be demonstrated. Small masses of epithelial cells and infrequently calculi were found in the lumen of these ducts. The ducts were lined by a low stratified epithelium, and the tracts of connective tissue surrounding them were somewhat increased in area and usually contained only small numbers of leukocytes. The intermediate-sized intrahepatic ducts also were frequently dilated, lined by a low stratified epithelium and in other respects also structurally resembled the major intrahepatic ducts. The interlobular hepatic ducts were infrequently dilated, and though most of the ducts of this class were lined by a simple epithelium, some were lined by a stratified epithelium of 2 or 3 cell layers. The lumen of the intermediate and interlobular ducts usually was free of debris. Further descriptions of the interlobular ducts and structures surrounding them are presented below.

Microscopically the changes in the liver of rats of Groups 1 and 2 which possessed dilated extrahepatic ducts were largely limited to the portal canals and the tissues immediately surrounding them. The area of the portal canals of the greater number of livers was slightly greater than normal. The canals contained a normal-sized artery, dilated vein, ducts varying from normal to greatly increased diameter, and greatly enlarged lymph vessels. The connective tissue of the portal canals

was loose in arrangement, edematous in appearance and contained fibroblasts with large vesicular nuclei. The connective tissue of the canals contained only small numbers of leukocytes, commonly of the heterophil variety. Pigment was not present, nor had multiplication of ducts occurred. Some of the hepatic cells bordering on the canal were swollen but none were surrounded by the tissues of the canal. Portal canals of this type undoubtedly represented an early stage of response to the biliary obstruction (Fig. 5).

In a small number of specimens, the portal canals of the liver had enlarged and expanded sufficiently to meet neighboring canals and, thereby, to surround the individual lobules of the liver (Fig. 6). In those canals the artery was normal, the vein usually distended and the interlobular duct irregular in outline and usually not readily distinguished from numerous masses of multiplying ducts. The multiplying ducts frequently composed the major part of the enlarged portal canals. The fibroblasts were enlarged or of normal size, and infiltrating heterophil leukocytes were variable in number but frequently quite numerous. Pigment was occasionally present in the tissues of the canals. Single or groups of hepatic cells were frequently surrounded by the connective tissues and multiplying ducts of the canals.

The degree of development of the lesions of the hepatic lobules varied considerably, but commonly was greatest for those which were surrounded by enlarged and anastomosed portal canals. In those lobules the bile cap-

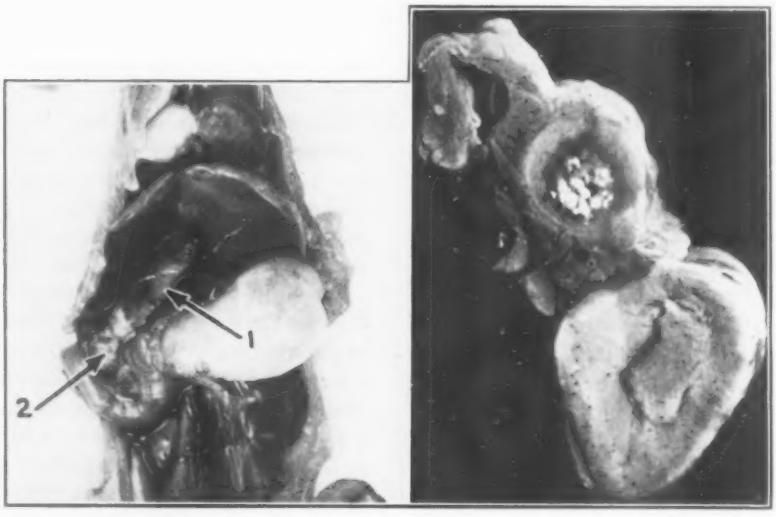

FIG. 1 FIG. 2

FIG. 1.—Ventral view of the liver and dilated bile ducts of a rat of Group 2 killed after 44 days on a diet deficient in vitamin A. Arrow 1 indicates the extrapancreatic portion of the common hepatic duct in which stones are visible; arrow 2 the intrapancreatic portion of the common hepatic duct.

FIG. 2.—Section showing the thickness of the wall, and the calculi and debris in the lumen of the common hepatic duct of a rat of Group 2 killed after 39 days on a diet deficient in vitamin A. Note the thickness of the epithelium, shown as an irregular dark band external to the calculi, and the abundant epithelial cell debris between the calculi (x 10).

laries were dilated, frequently blocked by bile thrombi, or ruptured into the space separating the hepatic cells and the lining of the sinusoids. The hepatic cells of the peripheral ends of the cell cords were swollen and possessed darkly stained nuclei while the cells in the middle and central portions of the cords were normal in size and appearance. Fatty infiltration of the hepatic cells was not found in any of our specimens though some of the cells possessed a foamy appearance. Excepting infrequent small areas, necrosis of the hepatic tissue had not occurred. Many hepatic cells were in mitosis. The lining cells of the peripheral end of the sinusoids were frequently enlarged, and groups of the cells appeared to fill the lumen. The cells lining the central and middle portions of the sinusoids were less frequently enlarged. Kupffer cells of all regions of the sinusoids frequently contained pigment granules. The central veins were commonly large and prominent, and the sinusoids were broadly continuous with them. In summary, the central and middle portions of the lobules were fairly normal in appearance and the pathologic features described above were best developed in the peripheral portion of the lobule.

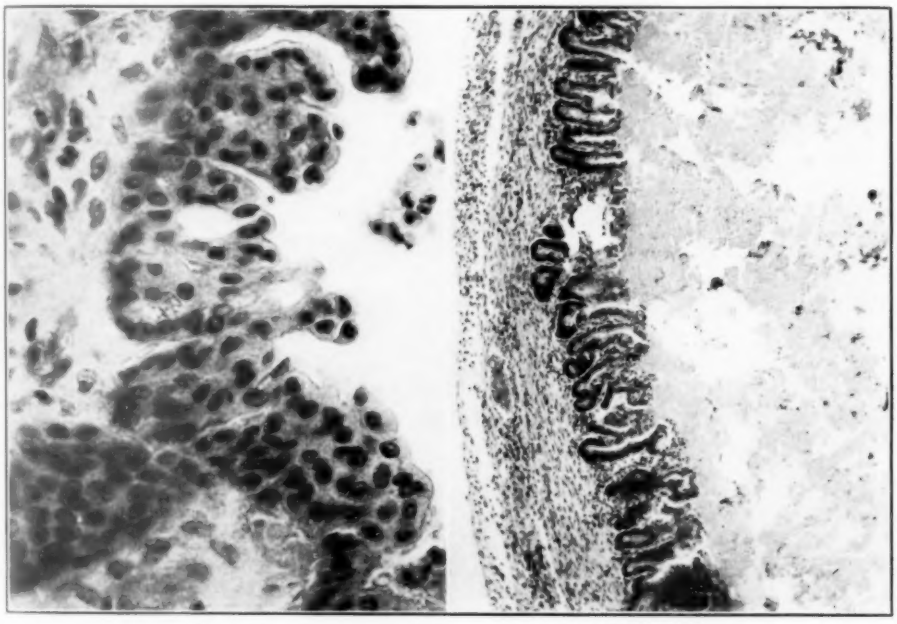

FIG. 3 FIG. 4

FIG. 3.—Early metaplasia and thickening of the epithelium of the dilated common hepatic duct of a rat of Group 2 killed after 41 days on a diet deficient in vitamin A (hematoxylin and eosin) (x 520).

FIG. 4.—Late metaplasia and thickening of the epithelium of the dilated common hepatic duct of a rat of Group 2 killed after 41 days on a diet deficient in vitamin A (hematoxylin and eosin) (x 90).

Comment. To our knowledge, the presence of dilated bile ducts and jaundice in rats with vitamin A deficiency has not previously been described. It is significant that a meta-

plasia of the epithelium similar to that which occurs in the epithelium of other organs in vitamin A deficiency was present in the dilated bile ducts of our animals with severe deficiency and jaundice. The metaplasia occurred in all regions of the extrahepatic biliary ducts and also in some segments of the intrahepatic ducts. The degree of metaplasia was not correlated with the size of the duct, but most likely was correlated with the length of time the deficiency had existed and the processes of metaplasia had been in operation. Varying degrees of obstruction of the passage from the common hepatic duct to the duodenum were established by the thickening of the epithelium and accumulation of the free masses of epithelial cells produced by the epithelium. Stasis of bile, jaundice, and the formation of calculus undoubtedly were the result of metaplasia of the epithelium. The presence of epithelial metaplasia in the enlarged ducts and its absence from ducts of control rats supplied vitamin A is in itself strong evidence that the conditions observed were the direct result of vitamin A deficiency.

The absence of fatty infiltration and necrosis from the liver indicates that deficiency of choline and cystine did not occur in our animals. Glynn and Himsworth[5] have shown that owing to the manner of distribution of portal blood to the liver, the left lobe may respond to borderline nutritional deficiency while other lobes of the liver do not. The left lobe of the liver did not differ from other lobes and borderline nutritional deficiency did not occur in our animals. The moderate degree of pathologic change of the portal

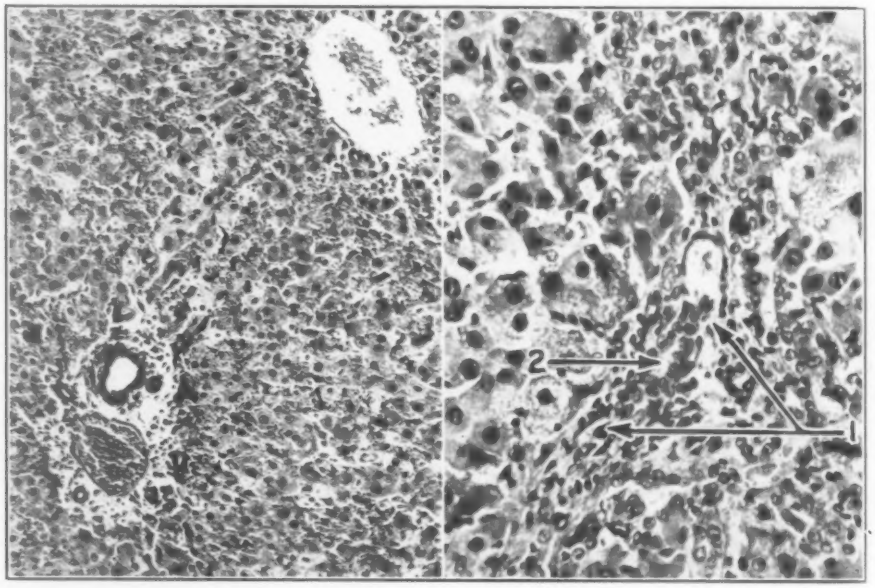

FIG. 5 FIG. 6

FIG. 5.—Portal canal of the liver of a rat of Group 1 killed after 34 days on a diet deficient in vitamins A and C (hematoxylin and eosin) (x 90).

FIG. 6.—Section adjacent to a portal canal of the liver of a rat of Group 2 killed after 41 days on a diet deficient in vitamin A (hematoxylin and eosin. Arrow 1 indicates the interlobular vein at the site of branching; arrow 2 designates the interlobular duct (x 300).

canals, and the absence of well-developed cirrhosis such as that observed by Higgins and Anderson[9] after ligation of the common hepatic duct of rats, show that biliary obstruction for our animals was not a complete one. This was also indicated by the absence of deep jaundice in many rats which possessed dilated bile ducts. In almost every detail, the pathologic changes of the bile ducts, excepting the metaplasia of the epithelium and liver observed in our rats, resembled the disease of uncomplicated partial obstruction and inconstant jaundice described for man by Himsworth[10].

Studies confirming the above-described observations have been completed and further studies of the nature of the disease condition observed in our rats with vitamin A deficiency are in progress.

Summary and Conclusions. A study has been made of the liver and bile ducts of rats with vitamin A deficiency and jaundice. Of 26 rats fed a deficient diet, 22 were continued on the diet long enough to experience symptoms of deficiency. Of the latter, 19 (86%) possessed dilated bile ducts and exhibited some degree of jaundice. Metaplasia of the epithelial lining occurred in all dilated extrahepatic ducts and many intrahepatic ducts. The metaplastic epithelium offered resistance to the flow of bile and produced free masses of cells which, by accumulating in the common bile duct and intramural duct, formed obstructions which resulted in stasis of bile and dilatation of the system of bile ducts. Obstruction and dilatation of the bile ducts were accompanied by a mild hypertrophy of the tissues of the portal tracts and moderate degenerative changes of the peripheral parenchymal tissues of the hepatic lobules. The metaplasia of the epithelium resembled that found in other organs in vitamin A deficiency, and indicates that this metaplasia is the primary result of the deficiency and the dilatation of the bile ducts and that the pathologic changes of the portal areas of the liver are secondary results of the deficiency.

Conclusions. 1. Metaplasia of the epithelium of the ducts of the biliary system occurs in vitamin A deficiency.

2. Detached masses of epithelial cells may obstruct the bile duct at the duodenal end and through resulting stasis of bile cause dilatation of the ducts.

3. Stasis of bile and dilatation of intrahepatic ducts are accompanied by hypertrophy of the portal tracts and limited degenerative changes of the peripheral portions of the lobules of the liver.

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REFERENCES

1. **Bessey, O. A.**, and **Wolbach, S. B.**: In: The Vitamins, pp. 27-54, Chicago, American Med. Assn., 1939.
2. **Bicknell, F.**, and **Prescott, F.**: The Vitamins in Medicine, 2d ed., New York, Grune & Stratton, 1946.
3. **Emiliani, P.**, and **Bazzocchi, G.**: Riv. di pat. sper., **10**, 72, 1933; Nutrition Abstr. and Rev., **3**, 392, 1933.
4. **Fujimaki, Y.**: Jap. Med. World, **6**, 29, 1926.
5. **Glynn, L. E.**, and **Himsworth, H. P.**: J. Path. and Bact., **56**, 297, 1944.
6. **Greene, E. C.**: Anatomy of the rat, Philadelphia, Am. Phil. Soc., 1935.
7. **Hart, G. H.**: Nutrition Abstr. and Rev., **10**, 261, 1940.
8. **Hendrickson, W. F.**: Bull. Johns Hopkins Hosp., **9**, 221, 1898.

9. **Higgins, G. M.**, and **Anderson, R. M.**: Arch. Path., **14**, 42, 1932.
10. **Himsworth, H. P.**: Lectures on the liver and its diseases. Cambridge, Harvard University Press, 1947.
11. **Mann, F. C.**: Anat. Rec., **18**, 355, 1920.
12. **Mann, F. C., Brimhall, S. C.**, and **Foster, J. P.**: Anat. Rec., **18**, 47, 1920.
13. **Mayer, J.**, and **Krehl, W. A.**: J. Nutrition, **35**, 523, 1948.
14. **Nylund, C. E.**, and **With, T. K.**: Vitamine u. Hormone, **2**, 7, 1942.
15. **Okey, R.**: Proc. Soc. Exp. Biol. and Med., **51**, 349, 1942.
16. **Robertson, E. C.**: Am. J. Med. Sci., **192**, 407, 1936.
17. **Saiki, T.**: Deut. med. Woch., **1**, 517, 1927.
18. **Schwegler, R. A., Jr.**, and **Boyden, E. A.**: Anat. Rec., **68**, 193, 1937.
19. **Stepp, W.**, and **Kühnau, J.**: Vitamine, Neue Deutsche Klinik, Berlin, Urban and Schwarzenberg, 1933.
20. **Tyson, M. D.**, and **Smith, A. H.**: Am. J. Path., **5**, 57, 1929.
21. **Wolbach, S. B.**: J. Am. Med. Assn., **108**, 7, 1937.
22. **Wolbach, S. B.**, and **Bessey, O. A.**: Physiol. Rev., **22**, 233, 1942.
23. **Wolbach, S. B.**, and **Howe, P. R.**: J. Exp. Med., **42**, 753, 1925.
24. Idem: Ibid., **57**, 511, 1933.

ELEVATED TITERS OF SERUM HETEROPHIL ANTIBODIES IN THREE INSTANCES OF MONOCYTIC LEUKEMIA*

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The definite statements by Fitzhugh and Weinstein[11] that low titers of heterophil antibodies are characteristic of leukemia and that high titers of these antibodies are not seen in that disease are generally accepted, and have been generally held (Bernstein[2]).

There are, however, 4 recorded instances in which high heterophil antibody titers have been observed in some association with probable leukemia. Bernstein[2] cited a dubious case (leukemia, or perhaps aplastic anemia) in which the titer reached 1:640. Kent[6] reported the case of an autopsied patient with monocytic leukemia having a Paul-Bunnell test ranging in titer from 1:4096 to 1:16,384. Proescher[7] reported a case (with autopsy findings) under the title of "Case of infectious mononucleosis with leukemoid blood picture in a boy four years old" in which constant great elevation of heterophil antibody titers were the basis for the diagnosis of infectious mononucleosis, but in which the described circulation of blastic cells in continued high proportion makes a diagnosis of leukemia more likely. Feldman and Yarvis reported the case of an 18 year old white male with cells typical of infectious mononucleosis. His heterophil titer was 1:512 with complete absorption by ox cells and no absorption with guinea pig kidney. During the 6 months illness the heterophil response became negative as the findings became those of lymphatic leukemia. Schultz[10], considering elevated heterophil titers in various conditions, reported titers of 1:45 or higher in 8 cases of myelogenous and 2 cases of monocytic leukemia. Absorption studies are not recorded.

This paper describes 3 additional instances of leukemia, all monocytic, in which elevated titers of heterophil antibodies were present. In 2 of the cases the absorption characteristics of the antibodies were studied.

Case 1. A. H. V., male, white, aged 40, admitted to the University of Chicago Clinics 5-16-35.

History. A. H. V. was well throughout his life until 2 months before admission, when

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he began to suffer weakness and lassitude, and lost about 15 lbs. in weight. For a month prior to admission there was swelling and soreness of gums, with hemorrhage therefrom, and shortly after this his vision became dim.

Physical Examination. The patient exhibited marked pallor and was undernourished. The fundus oculi on each side contained multiple hemorrhages. The gums were slightly swollen and very tender. The heart and lungs were normal. The spleen was felt 1 finger's breadth below the costal margin. The liver was not enlarged. The central nervous system was normal. There was slight enlargement of all lymph nodes.

Laboratory Findings. Urinalysis showed slight albuminuria. Wassermann reaction and Kahn reaction were negative. Ekg showed slight left axis deviation. Roentgen-ray examination of the chest was suggestive of slight mediastinal lymphadenopathy. Paul-Bunnell heterophil antibody test was positive 1:128 (serum dilution 1:512). Repeat test showed the same figure. Blood counts (on admission): Rbc 1,700,000; Wbc 59,600; Hgb. 32%; neutrophil polymorphs 2%; metamyelocytes 2%; myelocytes 2%; lymphocytes 25%; monocytes 60 to 69%. Of the monocytes, about two-thirds were very young forms, and frequent nucleoli were seen.

Progress. The patient died on 5-24-35, having shown progressive rise in the white cell count to 209,400. Fever was present throughout the hospital course. One dose of 0.3 gm. neoarsphemanine given on day of admission.

Autopsy (summary only). Monocytic leukemia, with leukemic infiltration by characteristic leukemic monocytes of axillary, inguinal, and all other lymph nodes, and of the lymphoid tissues of the ileum, cecum, and colon; of the liver, spleen, skin, kidneys, adrenals, thymus, heart, testis, bone marrow, thyroid, lungs, and palate. Gangrenous stomatitis. Multiple petechial hemorrhages throughout the body. Fatty degeneration of the heart. Bilateral bronchopneumonia.

Diagnosis. Monocytic leukemia, type Schilling (leukemic monocytic reticulendotheliosis.)

Discussion. This case was recorded prior to introduction of the absorption differentiation of heterophil antibodies.

Case 2. D. B., female, aged 30, married, a physician. Admitted to St. Vincent's Hospital, Los Angeles, 10-9-47.

Previous Health. No major illness other than whooping cough as a child.

Family Health. Both parents were allergic. Mother suffered from bronchial asthma. Father suffered from hay fever.

History of Illness. About 2 months prior to her admission to hospital the patient suffered from dryness and cracking of the nasal mucosa, which shortly swelled and assumed a gray color. An allergist was consulted and discovered positive skin tests to codein, brass, oats, wheat, soy, and a number of other miscellaneous items. The nasal condition was thought due to pollinosis, and vasoconstrictors gave relief for some time.

One month prior to admission mouth breathing became essential. The tongue, mouth, and pharynx became sore, and their mucous membranes were dull and grey. The gums were spongy but did not bleed. Coughing became distressful, induced vomiting, and became productive of thick, ropy mucus. A blood count showed Rbc 2,040,000 per c.mm.; hemoglobin level 40%, with 32,000 Wbc per c.mm.

A diagnosis of "subacute leukemia" was made and two 500 cc. blood transfusions were given, whereupon the patient was hospitalized for study.

Inventory Enquiry. There had been about 5 lbs. weight loss. There had not been fever. The skin had been normal. There had been no bony tenderness. The lymph nodes were not enlarged. Digestion was normal.

Physical Examination. The patient was a poorly nourished, tired, waxy looking woman. 5 feet, 6 inches in height; weight 114 lbs. The nose was greatly swollen but not painful. The nasal mucosa was a dull gray color. The nasal passages were completely occluded on both sides.

There were 2 small ulcers on the lips. On the tongue there was an 0.5 cm. shallow, gray ulcer. The mucosa of the hard palate was swollen and gray. The gums were purple in color and hypertrophied to a great degree.

The cervical lymph nodes were enlarged bilaterally. The anterior cervical nodes were tender. The occipital, post-auricular, axillary, and inguinal nodes were not enlarged.

The fundi oculi were normal. There were no abnormal findings related to the central nervous system.

The findings as to heart and lungs were normal. The liver and spleen were not enlarged.

Laboratory Findings. Urinalysis. sp. gr. 1.018, reaction alkaline, albumin trace, sugar none, acetone trace, microscopic showed normal sediment. Blood Kline negative. Blood culture negative.

Blood Counts. 10-10-47: Rbc 4,170,000. Hgb. 10.7 gm.; Wbc 24,150. Differential:

Polymorphonuclear neutrophils 20% (15% nonfilamented); eosinophils 1%; lymphocytes 17%; atypical monocytes 62%.

10-16-47: Rbc 3,850,000; Hgb. 9.4 gm.; Wbc 17,350. Differential: Polymorphonuclear neutrophils 18%; metamyelocytes 5%; lymphocytes 20%; monocytes 57% of which 16% were blast forms.

10-19-47: Rbc 3,600,000; Wbc 9,700. Differential: Polymorphonuclear neutrophils 29%; myelocytes 2%; promyelocytes 3%; basophils 1%; lymphocytes 24%; monocytes 41% with 18% blast forms.

Serologic Studies: Heterophil Antibody Titres

	Unabsorbed	Absorbed with Guinea Pig Kidney	Absorbed with Ox Cells
10-11-47	1:896		
10-14-47	1:896	1:20	1:160
10-18-47	1:224	0	1:56
10-31-47	1:112	0	1:56
Control Case of Infectious Mononucleosis Titer:			
10-14-49	1:1792	1:1792	0

Progress. The course downhill was characteristic of anemic leukemia and the patient died on 12-20-47 in a distant community without further study or opportunity for autopsy.

Diagnosis. Monocytic leukemia, Naegeli type; probable allergic diathesis.

Comment on Case. There is no reasonable doubt that this patient suffered from monocytic leukemia. She was believed to be an allergic subject. She had received 2 transfusions prior to the demonstration of the antibody reactions, but no liver extract or other foreign material. One transfusion had been followed by a febrile reaction.

Case 3. M. R., male, white, aged 52. Admitted to Birmingham Veterans Administration Hospital 1-2-49.

History. On admission he complained of pain in the left thigh and back in association with gross deformity of the left thigh following old injury. He gave a past history of bronchial asthma since 1917. No complaints were referred to the hematologic systems.

Physical Examination. Physical examination at the time of admission revealed a slightly dyspneic white male. Examination of the chest revealed numerous coarse rales in both bases. The expiratory phase of respiration was prolonged. There was marked deformity of the left lower extremity. Liver and spleen were not enlarged. There was no peripheral lymph node enlargement.

Laboratory Findings. On admission: Hgb. 14.7 gm.; Wbc 8,400; neutrophils 58; lymphocytes 36; monocytes 5; eosinophils 0; basophils 1.

Roentgen-ray. The left lower extremity revealed an old fracture of the femoral shaft below the base of the lesser trochanter, with complete avulsion of the trochanter and lateral and anterior angulation of the fracture site. There was a second healed fracture of the femoral shaft below its mid-portion. The chest film showed moderate generalized emphysema.

Course in Hospital. The patient was treated for his old fracture-avulsion with a left spica cast. He required treatment on several occasions for bronchial asthma.

On March 22, 1949, left posterior cervical lymphadenopathy developed with no apparent cause. This subsided with no specific treatment. The blood count at that time was normal.

About mid-April, 1949, he developed an evening elevation of temperature, the temperature ranging from 99.2° to 100.6°. He continued to be febrile. On May 10, 1949, it was noted that the posterior cervical nodes were large and discrete. The liver margin was felt 4 fingerbreadths below the right costal margin and the spleen was enlarged. A sternal marrow aspiration was performed and a diagnosis of monocytic leukemia (Naegeli type) was made. Heterophil antibody titer at that time was elevated.

Supportive therapy was provided, consisting of multiple blood transfusions, intravenous fluids, and aminophyllin as needed. Serial blood counts and hemoglobin showed a progressive anemia, and a gradual rise in the white count with marked increase in immature forms. Repeat heterophil tests showed continued elevated titer. Patient expired July 5, 1949.

Blood Counts. 4-17-49: Wbc 11,000; Hgb. 12.1 gm. Differential: Neutrophils 42%; lymphocytes 32%; monocytes 21%; basophils 5%.

5-10-49: Wbc 12,250. Differential: Neutrophils 56%, 5 of which were band forms, 1 promyelocyte, and 25 blasts; lymphocytes 22%; monocytes 14% with 3 promonocytes; eosinophils 2%; basophils 6%; platelet count 150,000; hematocrit 38 mm.

6-20-49 Rbc 3,780,000; Hgb. 11.1 gm.; Wbc 34,350. Differential: neutrophils 13% with 2 stabs and 1 promyelocyte; lymphocytes 18%; monocytes 66% with 8 promonocytes and 40 blasts; basophils 3%.

Sternal Marrow. 5-4-49: 54% "blast" forms; 5% promyelocytes; 6% myelocytes; 15% metamyelocytes of which 7.5% were basophils; 3%

mature granulocytes; 4.5% lymphocytes; 3.5% monocytes; 7% reticulum cells; 1.5% normoblasts; 1.5% basket cells.

Serologic Studies: Heterophil Antibody Titres

	Unabsorbed	Absorbed with Guinea Pig Kidney	Absorbed with Ox Cells
5-6-49	1:224		
5-12-49	1:896	1:28	1:14
Control: Infectious Mononucleosis			
6-12-49	1:896	1:896	0

Autopsy (Summary only). Microscopic examination of tissues removed at postmortem showed leukemic infiltrates in the liver, lymph nodes, spleen, myocardium and bone marrow. The typical cell was large, round to oval, with a nucleus which occupied a good portion of the cell, was deeply basophilic and irregular in outline. Many of these cells contained nucleoli.

Diagnosis. Monocytic leukemia (Naegeli type); bronchial asthma.

Comment on Case. This case represents another example of monocytic leukemia in an individual with a lengthy allergic background.

Discussion. The absorption characteristics of the different heterophil antibodies seen in the sera of abnormal persons, of those with serum sickness and of those with infectious mononucleosis were established by Davidsohn[3,4].

The percentage absorption of the various anti-bodies was obtained by Davidsohn in table on next column.

	Av. Titer	Pct. of Absorption by Beef Cells	Pct. of Absorption by G. P. Kidney
Normal antibodies (5 cases)	20	35%	100%
Serum sickness (3 cases)	91	97%	100%
Infectious mononucleosis (9 cases)	324	100%	69%

Thus, it would appear that the antibodies present in Cases 2 and 3 most closely resemble the "normal antibody" in their absorption properties. It is quite possible that the elevation in titers was due to the allergic diathesis evidenced by both patients, and was independent of the leukosis. In this connection it is recollected that Proescher's[7] patient had persistent eosinophilia. However, it has not been noted that the heterophil antibody titer is elevated in the allergic state[8,9] though Schultz[10] records a heterophil titer of 1:224 in an allergic individual. In leukosis it has been repeatedly shown that the antibody reactions as a whole are depressed. Thus, the low titer of antibodies seen in leukemia (Bernstein[1]) is probably due to low titers of the normal antibody. Absorption studies are not available covering this point. The possibility that the occasional leukemic might contract infectious mononucleosis is evident[5] but the absorption characteristics appear to preclude such an occurrence in these particular patients.

Summary. In leukemia, marked elevation of the heterophil antibody titers may occasionally occur. Thus far this has been noted most frequently in monocytic leukemia. In 2 cases, the antibodies were of the "normal" type of absorption characteristic.

REFERENCES

1. **Bernstein, A.**: J. Clin. Invest., **13**, 677, 1934.
2. **Bernstein, A.**: Medicine, **19**, 85, 1940.
3. **Davidsohn, I.**: J. Am. Med. Assn., **108**, 389, 1937.
4. **Davidsohn, I.**, and **Walker, P.**: Am. J. Clin. Path., **5**, 455, 1935.
5. **Feldman, F.**, and **Yarvis, J. J.**: New York State J. Med., **44**, 1693, 1944.
6. **Kent, C. F.**: Am. J. Clin. Path., **10**, 576, 1940.
7. **Proescher, F.**: Path. and Bact. Sect., Cal. State Med. Assn. Meeting, 8 May, 1944.
8. **Randolph, T. G.**, and **Hettig, R. A.**: Am. J. Med. Sci., **209**, 306, 1945.
9. **Randolph, T. G.**, and **Gibbons, E. B.**: Ibid., **207**, 638, 1944.
10. **Schultz, L. E.**: Arch. Int. Med., **81**, 328, 1948.
11. **Weinstein, G. L.**, and **Fitz-Hugh, T.**: Am. J. Med. Sci., **190**, 106, 1935.

THE EFFECT OF PROCAINE ADMINISTERED INTRAVENOUSLY ON THE CUTANEOUS PAIN THRESHOLD

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The use of intravenous procaine as an analgesic has received increasing attention over the past ten years. After its first description in 1908 by Bier[4] this route of administration for procaine was virtually ignored until 1938 when Lundy[15] reported its value as an antipruritic in patients with obstructive jaundice. Then followed in rapid succession reports of its clinical application as an analgesic in the management of burns[3,6], postoperative discomfort[5,13,15], labor[1,2,12], sprains, fractures and arthritis[7,9], and numerous other painful conditions[8]. So widespread has been its suggested use and so promising the results that one investigator commented: "We are still searching for any kind of severe pain which cannot be relieved by procaine intravenously"[1].

Despite this enthusiastic acceptance of the effectiveness of such therapy, published reports reveal an uncritical evaluation of the results. As Rovenstine and Papper[18] have recently observed, both individual (internal) and group controls are lacking. There is no series in which procaine solution has been alternated with saline and the effects compared; and in some of the studies other analgesics or sedatives were given with the procaine.

The problem is complicated further by the paucity of laboratory data on the basic site and modes of action of procaine or its derivatives in pain syndromes. Allen *et al.* have proposed that procaine is concentrated at the site of injury, where exudation and edema formation are in progress[2]. Graubard and Peterson[9] report that intravenous procaine is concentrated 7 to 8 times more in traumatized than in normal tissue; they conclude that here it acts directly on nerve fibers or endings. In view of Allen's proposal, and in order to secure some quantitative measure of the analgesic properties of intravenous procaine, this study of the effect of intravenous procaine on the pain threshold in both traumatized and normal skin was designed. The pain threshold is the only aspect of pain that has been opened to accurate measurement: its determination in man by the Hardy-Wolff-Goodell technique, using a radiant heat stimulus, has already proven useful in the study of analgesic agents[11,12].

Two recent investigations are particularly relevant to this problem. Bigelow and Harrison[5] have reported a variable elevation of the pain threshold after the subcutaneous injection of 5 to 40 cc. of 2% procaine elsewhere in the body, but the data are inconclusive. Papper *et al.*[17] have observed that intravenous procaine induces only an insignificant rise in the pain threshold

of normal skin, leaving unanswered the pertinent question of the effect of the drug upon pain perception in injured tissue.

Method. In 4 subjects, healthy male medical student volunteers between the ages of 24 and 27, a first degree burn was produced by exposure to ultraviolet radiation in an area approximately 6 cm. by 4 cm. on the volar surface of the forearm. The exposure was 4½ minutes in duration with the lamp at a distance of 20 inches, a technique which invariably produced maximum erythema without vesiculation. Skin thus prepared was hyperalgesic, that is, tender to light pressure and unusually sensitive to pin prick or other noxious stimuli. The subjects were then indoctrinated into the use of the Hardy-Wolff-Goodell[11] apparatus for measurement of cutaneous pain threshold to a radiant heat stimulus. Each subject was not regarded as indoctrinated until he showed a variation of no more than ± 5% in his report of the end point. In all subjects the opposite forearm was used as a control area of normal skin. One modification of the Hardy-Wolff-Goodell technique was made; on the hyperalgesic area, threshold pain was defined as the faintest burning pain perceived, since the threshold for "pricking" pain was so far above that for burning pain that it was obscured and difficult to determine. On the normal skin area "pricking" pain was taken as threshold since this was almost always the first type of pain perceived.

After indoctrination and while the hyperalgesia of the burn was still at its height 1.0 gm. of procaine hydrochloride in 500 to 1000 cc. of physiological solution of sodium chloride was administered by infusion into a leg vein. Pain thresholds on the normal and hyperalgesic skin areas were measured before, during, and after the administration of the drug. All observations were made in a quiet room at a constant temperature.

Results. As indicated in the table, the degree of induced erythema was sufficient to lower the pain threshold to 50% or less of normal. In both the normal and the hyperalgesic burned skin, particularly in the latter, the pain threshold was elevated during the period of administration of the procaine solution, but to only a slight extent, except for a 24% rise in the threshold of the hyperalgesic skin of one subject.

Such responses are of borderline significance, particularly since in the hyperalgesic skin a rise in threshold of only 20 millicals. per cm.² per sec. becomes disproportionately large when expressed as a percentile change. Moreover, soon after the infusion was completed the thresholds returned to the base-line or to lower levels.

The results are summarized in graphic form in Fig. 1. Although the number of subjects and observations

TABLE 1.—SUMMARY OF DATA

Subject	Amount and Concentration of Procaine	Duration of Administration (min.)	Control Pain Threshold*		Pain Threshold during and after Procaine Administration				
			Burned Skin	Normal Skin	Time of Measurement after beginning of Procaine Injection (min.)	Burned Skin		Normal Skin	
						Threshold	% Change	Threshold	% Ch
M. H.	500 cc. of a 0.2% Sol.	65	105	270	30	120	+14	280	+3
					45	130	+24	—	
					60	—	—	280	+3
					120	110	+5	270	0
P. G.	1000 cc. of a 0.1% Sol.	90	110	250	60	120	+9	—	—
					70	—	—	250	0
					130	120	+9	250	0
					155	120	+9	—	—
D. S.	500 cc. of a 0.2% Sol.	60	140	250	30	145	+3.6	—	—
					45	—	—	260	+4
					80	130	−7	250	0
					120	140	0	250	0
E. S.	1000 cc. of a 0.1% Sol.	55	105	265	50	110	+5	280	+6
					145	80	−24	270	+2
					190	90	−9	270	+2

* Pain thresholds are measured in response to a controlled radiant heat stimulus (Hardy-Wolff-Goodell technique) and are expressed in millicals./cm.² sec.

is relatively few, the responses show a consistency which is informative.

Discussion. From the above data it is apparent that only during its administration did procaine raise the pain threshold, and then merely to a trivial degree. Even this minor rise in threshold can perhaps be related to the fact that all subjects complained of an impairment in ability to concentrate during the procaine infusion. A considerable degree of attention is necessary for power evaluation of the pain threshold and the mental lethargy which the subjects noted may well have altered their responses. Nonetheless, the return of the pain thresholds to, or below, control levels shortly after completion of the intravenous administration is highly significant in view of the clinical claims that procaine can ease pain as long as 5 to 12 hours after administration.

There is obviously, then, a notable difference between the effect of procaine on the pain threshold and its reported effect on pain syndromes. This discrepancy may be due in part at least to uncritical clinical observation, but several other possible explanations merit consideration:

1. The ability of an agent to diminish the intensity of pain from suprathreshold stimuli usually parallels its ability also to raise the pain threshold[19]. This holds true for analgesics, such as acetylsalicylic acid and codeine, which act centrally. It is conceivable, however, that procaine administered intravenously can lessen the intensity of pain without raising the pain threshold. This might result: *a*, if procaine were able to block or neutralize a noxious metabolite, the hypothetical pain (or "P") substance present in tissues subjected to sustained injury; and *b*, if the

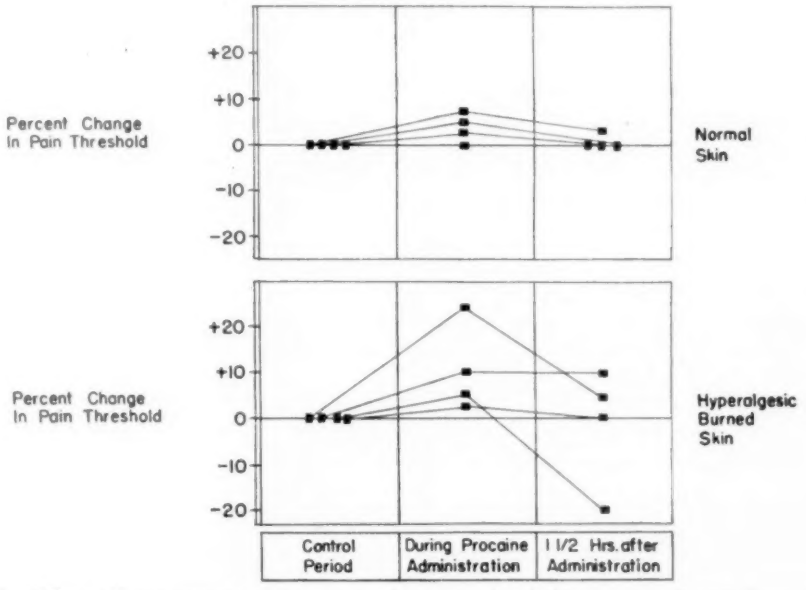

FIG. 1.—Effect of intravenous procaine on the pain threshold in normal and hyperalgesic burned skin.

pain substance were not essential as a mediator of the fleeting pain of the pain-threshold measurement.*

2. The tissue injury produced in these experiments may have been too mild and superficial to permit the detection of a procaine effect. The limitation of the trauma to a non-painful first degree burn was necessary, however, for any spontaneous lasting pain would have made threshold measurements impossible by the technique employed.

3. The reputed benefit of procaine in clinical pain syndromes may sometimes be other than simply analgesic. The drug may act by alteration of local factors, such as blood flow, or by as yet unevaluated central effects.

None of these explanations can yet conclusively resolve the difference between the results of laboratory experiment and bedside observation. The ultimate evaluation of any analgesic technique still depends upon the patient in pain. The answer in the case of intravenous procaine awaits controlled clinical test.

Summary and Conclusions. One gram of procaine administered intravenously over a period of 55 to 75 minutes to adult human subjects was ineffective in significantly raising the pain threshold to radiant heat in either normal or traumatized skin.

These results are contrasted with reports of the dramatically effective analgesic action of procaine given intravenously for the control of clinical pain.

Several possible explanations for this discrepancy are advanced. A need is apparent for a critical and objective evaluation of intravenous procaine in pain syndromes.

REFERENCES

1. **Allen, F. M.**: Am. J. Surg., **70**, 283, 1945.
2. **Allen, F. M., Crossman, L. W.**, and **Lyons, L. V.**: Anesth. and Analg., **25**, 1, 1946.
3. **Barbour, C. M.**, and **Tovell, R. M.**: Anesthesiol., **9**, 514, 1948.
4. **Bier, A.**: Berl. klin. Woch., **46**, 477, 1909.
5. **Bigelow, N.**, and **Harrison, I.**: Pharmacol. and Exp. Ther., **81**, 368, 1944.
6. **Brittain, G. J. C.**: Anaesthesia, **4**, 30, 1949.
7. **Gordon, R. A.**: Canad. Med. Assn. J., **49**, 478, 1943.
8. **Graubard, D. J., Robertazzi, R. W.**, and **Peterson, M. C.**: N. Y. State J. Med., **47**, 2187, 1947.
9. Idem: Anesth. and Analg., **27**, 222, 1948.
10. **Graubard, D. J.**, and **Peterson, M. C.**: Anesthesiol., **10**, 175, 1949.
11. **Hardy, J. D., Wolff, H. G.**, and **Goodell, H.**: J. Clin. Invest., **19**, 649, 1940.
12. Idem: Proc. Research Nerv. and Ment. Dis., **23**, 1, 1943.
13. **Johnson, K.**, and **Gilbert, C. R. A.**: Anesth. and Analg., **25**, 133, 1946.
14. **Kraft, K. A.**: Canad. Med. Assn. J., **57**, 350, 1947.
15. **Lundy, J. S.**: Clinical Anesthesia, Philadelphia, W. B. Saunders, 1942.
16. **McLachlin, J. A.**: Canad. Med. Assn. J., **52**, 383, 1945.
17. **Papper, E. M., Brodie, B. B., Lief, P. A.**, and **Rovenstine, E. A.**: N. Y. State J. Med., **48**, 1711, 1948.
18. **Rovenstine, E. A.**, and **Papper, E. M.**: Bull. N. Y. Acad Med., **25**, 298, 1949.
19. **Wolff, H. G.**, and **Hardy, J. D.**: Physiol. Rev., **27**, 167, 1947.

* In the course of a separate and as yet unpublished investigation we have observed that intravenous procaine does not alter pain intensity in, or the spread of pain from, a finger immersed in water at 0° C.

THE EFFECT OF A FAT-FREE DIET IN CAUSING LOW SERUM CHOLESTEROL

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While treating ulcerative colitis in this hospital with a diet consisting of protein hydrolysate and dextrimaltose, tests of liver function were sometimes performed. It was observed that patients on this regimen had remarkably low serum cholesterol concentrations. Since many investigators have implicated cholesterol metabolism in the pathogenesis of arteriosclerosis[5,6,8], we decided to see if the random observations reflected a consistent effect of this synthetic fat-free diet. The latter, when supplemented with essential vitamins and iron, has been found satisfactory in maintaining nutrition and health[9,10].

TABLE 1. THE FALL IN SERUM CHOLESTEROL CONCENTRATION ON A DIET OF PROTEIN HYDROLYSATE AND DEXTRIMALTOSE.

Case No.	*Age/Sex*	*Diagnosis*	*Days on Special Diet*	*Serum Cholesterol Concentration (Mg.%)*		
				Initial Level	*Lowest Level Attained*	*Decrease*
1	57/M	Diverticulitis	7	176	116	60
2	29/M	Gastric Ulcer	5	92	87	5
3	29/M	Enteritis	8	216	142	74
4	64/M	Duodenal Ulcer	13	382	256	126
5	33/F	Duodenal Ulcer	18	233	168	65
6	27/M	Ulcerative Colitis	53	187	87	100
7	52/M	Duodenal Ulcer	16	260	232	28
8	60/M	Duodenal Ulcer	16	198	142	56
9	67/M	Gastritis	13	187	149	38
10	51/M	Duodenal Ulcer	14	286	160	126
11*	53/M	Duodenal Ulcer	13	263	167	96
12	60/F	Esophageal Ulcer	5	347	324	23
13	60/M	Esophageal Ulcer	11	353	184	169
14	65/M	Duodenal Ulcer	18	203	107	96
Minimum	29	—	5	92	87	5
Maximum	67	—	53	382	324	169
Average	51	—	15	256	171	85

* Patient 11 drank, in addition to the protein hydrolysate-dextrimaltose, 540 cc. of a milk and cream mixture daily. This mixture contained 68 gm. of fat per day.

* Smith, Kline and French Fellow in Gastroenterology.

Procedure. The subjects were 14 patients admitted to the medical service of this hospital for protein hydrolysate therapy of benign lesions of the gastrointestinal tract (Table 1).

The cholesterol concentration in serum was determined in each patient before therapy was begun or, in a few instances, 2 or 3 days afterward. Subsequent cholesterol measurements were made 2 or 3 times a week during the period of special alimentation, and at least several times after the resumption of ordinary foods. Cholesterol esters were determined serially in 3 cases.

The serum cholesterol determinations were made by means of a technique developed in this hospital, utilizing color produced by cholesterol in chloroform solution with acetic anhydride and sulfuric acid under controlled conditions of time and temperature. Color densities were read in an electric photometer. Cholesterol was extracted from serum by means of alcohol and ether as described by Bloor[1]. The esterified cholesterol was determined after precipitation of free cholesterol as digitonide. The precision of the method was ± 6.7 mg. per 100 ml.† Cholesterol in samples of serum of apparently normal individuals when examined by this method ranged from 110 to 355 mg. per 100 ml. (average 220).

The duration of treatment ranged from 5 to 55 days. The protein hydrolysate and dextrimaltose were given together in water, the solution containing 15 to 30% of each compound. Each day 2,200 to 4,000 calories

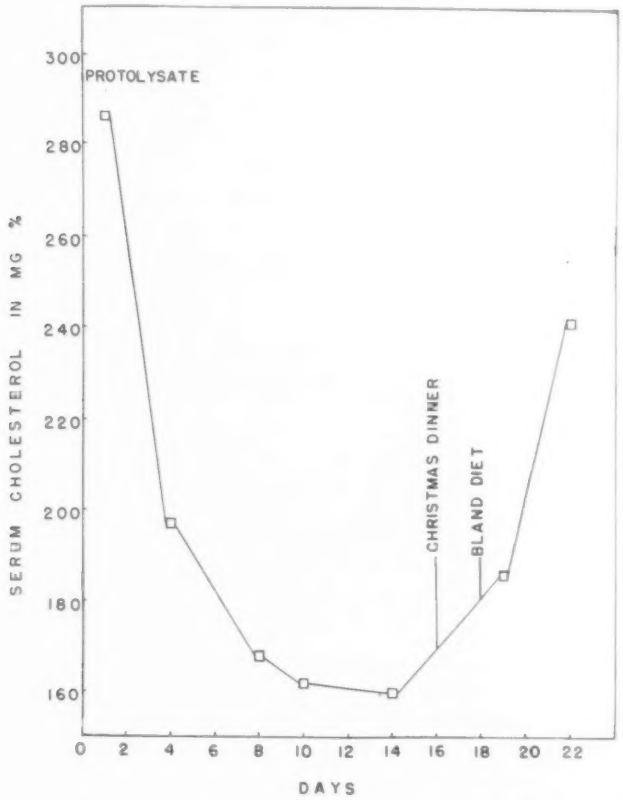

FIG. 1.—The concentration of the serum cholesterol in a patient while consuming protolysate-dextrimaltose and after resumption of a bland diet.

† Calculated as sigma (duplicates) $= \sqrt{\frac{(x-y)^2}{2n}}$ where x and y are the results of duplicate determinations and n is the number of pairs.

were thus supplied. All of the patients either gained or maintained weight on this regimen. Polyvitamin capsules and ferrous sulfate were administered, but no other medications were given except barbiturates or atropine as required for symptomatic relief.

Results. A fall in the serum cholesterol concentration well beyond the range of experimental error occurred in 13 of the 14 patients (Table 1). The fall in most instances was greater when the initial cholesterol value was relatively high. The decrease in serum cholesterol concentration averaged 85 (5 to 169) mg. per 100 ml. in 15 days.

The changes in serum cholesterol concentration in response to alterations in diet were very rapid. The average number of days in which serum cholesterol fell 20 mg. per 100 ml. or more was 5 (range 3 to 7). After resumption of an ordinary diet the average number of days in which the cholesterol rose 20 mg. per 100 ml. or more was 8 (range 2 to 16). The speed of these changes is illustrated in Figs. 1 and 2.

The concentration of the serum cholesterol esters changed in the same direction as did the total cholesterol (Fig. 2). Expressed as per cent of total serum cholesterol concentration, the cholesterol esters fell an average of 10% while the cholesterol was falling and returned to the original percentage when the cholesterol reached its initial level.

Comment. The failure of the serum

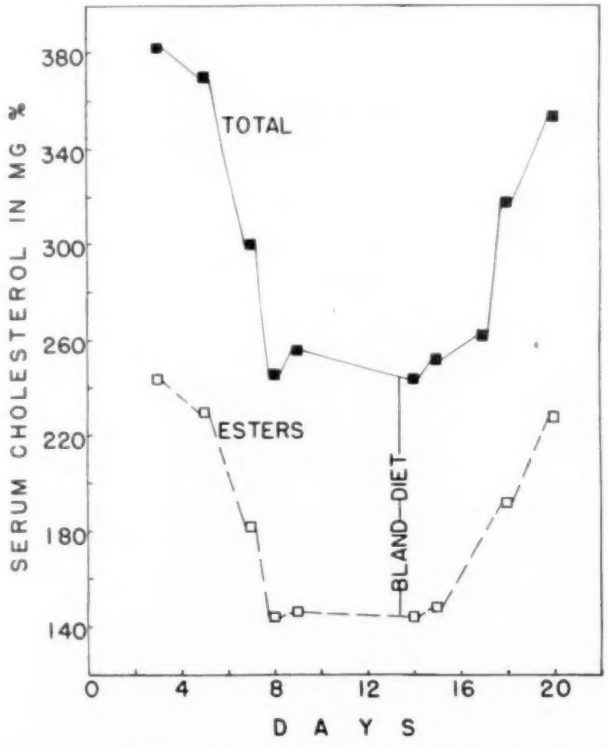

FIG. 2.—The concentration of the serum cholesterol and cholesterol esters in a patient consuming protolysate-dextrimaltose and after resumption of a bland diet. Total cholesterol is represented by solid squares and solid line. Cholesterol esters are represented by open squares and broken line.

cholesterol to fall in one patient (Case 2) requires comment. This patient, who had a large benign gastric ulcer, had been vomiting daily and had lost 29 pounds of body weight in the 2 months prior to hospitalization. Serum cholesterol on admission and before the special alimentation regimen was 92 mg. per 100 ml. It was 87 mg. per 100 ml. by the sixth day of alimentation. The initial low level is consistent with the observation that the blood cholesterol falls in malnutrition[11]. In nearly absolute starvation the serum cholesterol rises, but if as little as 40 or 50 gm. of carbohydrate are consumed daily, or just enough to prevent ketosis, the serum cholesterol does not rise; on the contrary, it falls[7]. The fact that this patient's serum cholesterol did not fall below 87 mg. per 100 ml. suggests that there is a limit beyond which diet will not readily lower the cholesterol level. It is interesting that another patient (Case 6), who was on protolysate for the longest period (53 days), had a fall in cholesterol to 87 mg. per 100 ml.

Obviously, even in short periods, this protolysate-dextrimaltose diet markedly lowers the serum cholesterol. The regimen, however, is not practical for long periods of time except when special indications exist. Nevertheless it provides a means for the study of basal cholesterol metabolism.

The mode of action by which this diet lowers the blood cholesterol is not known and is to be investigated. Some of the possibilities are as follows:

1. The absence of cholesterol.

2. The absence of fat. The absorption of cholesterol from the intestine is said to be largely dependent upon the simultaneous absorption of fatty acids[2,6]. On a fat-free diet one would expect a minimum of fatty acids in the intestine, since only those excreted would be present. The reduction in fatty acid absorption might be of prime importance, since ordinarily most of the cholesterol in the human intestine is carried there in bile or leukocytes, and does not come from food[6]. Absence of lipid from food may require secretion of additional sterol by the intestine and thus lower the amount in the serum.

3. The high protein intake may alter the bacterial flora of the bowel. An increased growth of those organisms responsible for the conversion of cholesterol into the non-absorbable coprosterol[4] may conceivably occur on this regimen.

4. The high protein diet, through its specific action, may alter metabolism in some more fundamental way. It has been reported that Eskimos who consume large quantities of fat and at times eat as much as 5 lbs. of meat daily have a relatively low concentration of cholesterol in the serum[3]. Their basal metabolic rates are uniformly high on the basis of American standards.

It is of interest that one patient (Case 11) drank, in addition to the protein hydrolysate-dextrimaltose mixture, a quantity of milk and cream containing 68 gm. of fat daily. Nevertheless, his serum cholesterol fell appreciably. It may be possible, therefore, to construct a dietary consisting of more palatable foods which, when ingested, would maintain a low serum cholesterol concentration.

Summary. 1. The serum cholesterol concentration is rapidly and markedly lowered by an alimentation regimen consisting entirely of protein hydrolysate and dextrimaltose.

2. Upon resumption of a diet of ordinary foods, there is a return of the serum cholesterol to initial levels.

3. Possible mechanisms of reduction in serum cholesterol by dietary means are discussed.

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REFERENCES

1. **Bloor, W. R.**: J. Biol. Chem., **24**, 227, 1916.
2. **Cook, R. P.**: Biochem. J., **30**, 1630, 1936.
3. **Corcoran, A. C.**, and **Rabinowitch, I. M.**: Ibid., **31**, 343, 1937.
4. **Dam, H.**: Ibid., **28**, 820, 1943.
5. **Gofman, J. W.**, **Lindgren, F.**, **Elliott, H.**, **Mantz, W.**, **Hewitt, J.**, **Strisower, B.**, **Harring, V.**, and **Lyon, T. P.**: Science, **111**, 166, 1950.
6. **Gubner, R.**, and **Ungerleider, E.**: Am. J. Med., **6**, 60, 1949.
7. **Kartin, B. L.**, **Man, E. B.**, **Winkler, A. W.**, and **Peters, J. P.**: J. Clin. Invest., **23**, 824, 1944.
8. **Kempner, W.**: Bull. N. Y. Acad. of Med., **22**, 358, 1946.
9. **Machella, T. E.**: Am. J. Med., **7**, 191, 1949.
10. **Machella, T. E.**, and **Miller, T. G.**: Gastroenterology, **10**, 28, 1948.
11. **Man, E. B.**, and **Gildea, E. F.**: J. Clin. Invest., **15**, 203, 1936.

PITUITARY VERSUS PRIMARY THYROID MYXEDEMA

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In 1940, Means, Hertz and Lerman[12] reported a series of myxedematous patients who showed evidence of associated gonadal and adrenal cortical insufficiency and did not respond to thyroid therapy in the usual manner. They postulated a pituitary etiology and distinguished these patients from others with primary thyroid myxedema. These criteria have been accepted by most investigators; as recently as this year (1950), Tucker *et al.*[16] diagnosed pituitary myxedema in 3 patients on this basis. In order to test the validity of this thesis, we have evaluated adrenal cortical function in 12 consecutive patients with frank myxedema. To our surprise adrenal cortical deficiency was present in every instance, whether the primary etiology was pituitary or thyroid, so that a differential diagnosis on this basis was therefore impossible.

Case Reports. Case 1. F. G., a 52 year old negress, was first seen in this clinic following thyroidectomy for a substernal goiter in 1942, after which signs and symptoms of hypoparathyroidism developed. This was well controlled with Vitamin D, 200,000 units daily. She complained of fatigue, cold intolerance and constipation. Examination revealed a cool, dry, scaly skin, and loss of axillary and eyebrow hair. Blood pressure was 126/80, pulse 75. The BMR was −14%, blood cholesterol 359 mg. %, and the 24 hour I^{131} uptake by the thyroid gland 9%. Roentgen-ray: minimal cardiac enlargement, no pericardial effusion, and normal sella. Apparent onset: 1942. Clinical diagnosis: primary thyroid myxedema, post-thyroidectomy.

Case 2. C. G., a 35 year old negress, was made myxedematous while being treated with methyl thiouracil for hyperthyroidism. She complained of somnolence, lethargy and dry skin. Her BMR was −28%, cholesterol 504 mg. %. Apparent onset: 2 months. Clinical diagnosis: primary thyroid myxedema (secondary to methyl thiouracil overdosage).

Case 3. W. B., a 36 year old negress, complained of somnolence, lethargy, obesity, hypomenorrhea and cold intolerance. Her skin was dry and myxedematous, and periorbital edema and depression of mental faculties were marked. Blood pressure was 188/120, pulse 80. The BMR was −25%, blood cholesterol 460 mg. %, and I_{131} uptake by the thyroid gland 6% in 24 hours. Roentgen-ray examination revealed an enlarged heart. Apparent onset: September 1947. Clinical diagnosis: primary thyroid myxedema.

Case 4. C. M., a 57 year old white female, complained of constipation, anorexia, hoarseness of the voice and intolerance to cold. She showed dry, thick, yellow skin, scant axillary, head and pubic hair, somnolence, lethargy, and mental dullness. Blood pressure was 160/108, pulse 60. The BMR was −46%, and blood cholesterol 395 mg. %. Apparent onset: 1942. Clinical diagnosis: primary thyroid myxedema.

Case 5. L. J., a 64 year old white female, complained of itching of the skin and hoarseness of the voice. Examination revealed a thick, dry, yellow skin infested with scabies, marked periorbital edema, sparseness of head, axillary and pubic hair, somnolence, lethargy, and mental dullness. Blood pressure was 160/80, pulse 80. The BMR was −25%, blood cholesterol 291 mg. %, and 24 hour I_{131} uptake by the thyroid gland 12%. Roentgen-ray: enlarged heart, and normal sella turcica. Apparent onset: 1946. Clinical diagnosis: primary thyroid myxedema.

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CASE 6. P. K., a 57 year old white female, complained of exertional dyspnea and cold intolerance. She was known to have syphilitic heart disease. Physical examination revealed dry, thick, yellow skin, periorbital edema, scant pubic, axillary and head hair, hoarseness of the voice, and mental dullness. Blood pressure was 154/84, pulse 88. The BMR was −30%, cholesterol 235 mg. %, and 24 hour I_{131} uptake 4%. Roentgen-ray: pericardial effusion, and normal sella. Apparent onset: 1946. Clinical diagnosis: primary thyroid myxedema.

CASE 7. A. H., a 60 year old white male, complained of weakness, anginal pains, progressive loss of hearing, constipation and hoarseness. Physical examination showed dry, thick, yellow skin, generalized hair loss and marked mental dulless. Blood pressure was 120/76, and pulse 64. Auricular fibrillation was apparent on ECG. The BMR was −50%, blood cholesterol 558 mg. %, and 24 hour I_{131} uptake 3%. Roentgen-ray: no cardiac enlargement and normal sella. Apparent onset: 1947. Clinical diagnosis: primary thyroid myxedema.

CASE 8. A. S., a 62 year old white female, complained of cold feet, dry skin, fatigue, hoarse voice and cold intolerance. She had gained 12 pounds in the year preceding these studies. Her skin was dry, scaly, cold and had a yellow tinge. Periorbital edema and hoarseness were marked. Head hair was dry and brittle and axillary and eyebrow hair scant. Blood pressure was 158/90, pulse 60. Cholesterol was 516 mg. %. Roentgen-ray: sella at upper limits of normal. Apparent onset: 1944. Clinical diagnosis: primary thyroid myxedema.

CASE 9. J. M., a 36 year old negress, complained of periods of amenorrhea (up to 4 months) and cold intolerance. She was short (4 feet, 6 inches) and looked like a typical cretin. Physical examination revealed thick dry skin, periorbital edema, sparse pubic, axillary and head hair, poorly developed breasts, and mental retardation. Blood pressure was 100/64, and pulse 80. The BMR was −14% (poor test), cholesterol 312 mg. %, and 24 hour I_{131} uptake 7%. Roentgen-ray: delay in bone age as evidenced by ununited epiphyses; normal sized heart, and enlarged sella. Apparent onset: birth. Clinical diagnosis: primary thyroid myxedema (Cretinism).

CASE 10. M. R., a 35 year old white female, complained of amenorrhea, fatigue, and anorexia since the birth of a child 18 months before. In addition, she had developed a depressive psychosis. She had dry, cool skin, absent axillary and scant pubic hair. She was somnolent and dull and responded slowly to questioning. Blood pressure was 130/80, and pulse 75. The BMR was −31%, cholesterol 646 mg. %, and 24 hour I_{131} uptake 5%. Roentgen-ray: normal sized heart and normal sella. Apparent onset: 1947. Clinical diagnosis: pituitary myxedema.

CASE 11. V. H., a 40 year old negress, complained of pain in the legs, constipation and cold intolerance. Menses had been regular until 1947 with no periods since. She claims to have been pregnant 4 times, each ending in a spontaneous miscarriage at 2 to 3 months. Physical examination revealed a short (4 foot, 6 inches) woman with dry cool skin, scant axillary and pubic hair, but with good breast development. Blood pressure was 96/66, and pulse 80. The BMR was −24%, cholesterol 178 mg. %, and 24 hour I_{131} uptake 5%. Roentgen-ray: marked pericardial effusion, atonic sigmoid colon, and slightly enlarged sella. Apparent onset: 1947. Clinical diagnosis: pituitary myxedema.

CASE 12. J. Z., a 25 year old acromegalic white male, complained of fatigue, lethargy and cold intolerance. Acromegaly was first noted in 1944, but had not progressed since 1947, when the above symptoms commenced. He showed dry yellow skin, periorbital edema, dry sparse hair and mental dullness. Blood pressure was 110/74 and pulse 75. The BMR was −47% and blood cholesterol 228 mg. %. Roentgen-ray: enlargement of the sella with destruction of the floor; no enlargement of the heart. Apparent onset: 1947. Clinical diagnosis: pituitary myxedema (acromegaly, inactive).

Methods. The adrenal glands of these patients were studied with reference to their 3 major functions. The DOCA-like fraction, which influences electrolyte and water metabolism, was evaluated by means of serum sodium, potassium and chloride determinations, as well as by the ability of the kidney to excrete water, chloride and urea after hydration[13]. The S-hormones were measured in the urine[2]. Insulin tolerance[6] tests were performed and in addition to fasting eosinophil levels the drop in eosinophil count 4 hours after the production of hypoglycemia[15] was observed. N-hormone production

TABLE 1.—SUMMARY OF LABORATORY STUDIES.

		Normal Range	1. F.G.	2. C.G.	3. W.B.	4. G.M.	5. L.J.	6. P.K.	7. A.H.	8. A.S.	9. J.M.	10. M.R.	11. V.H.	12. J.Z.
Thyroid	BMR—%	+15–15	−14	−28	−26	−46	−25	−30	−50		−14	−31	−24	−47
	Cholesterol - mg.%	110–300 (aver. 200)	359	504	460	395	291	235	558	516	312	646	178	228
	Iu Tracer—%	15–35	9		6		12	4	3		7	5	5	
	DOCA-Like Hormones													
Adrenals	Sodium-mEq/l	128–151 (aver. 140)	135	149	136	135	155	149	144	150	146		156	133
	Potassium-mEq/l	4.3–5.3 (aver. 4.8)	4.3	4.8	5.0	4.6	4.7	4.3	4.5	4.4	4.6	4.1		5.1
	Chloride-mEq/l	97–106 (aver. 101)	96	91	96	92	107	84	98	102	97		91	94
	A-value	25 or greater				10	Norm		<10		16			26
	S-Hormones													
	11-oxysteroids-mg./24 hrs.	0.9–2.0	0.6	0.6	0.2	0.5	0.3		0.5		0.2	0.7		0.3
	Insulin Tolerance Test	Not over 50% decrease in 30 min., returning to fasting in 60–90 min.												
	Fast. Bl. Sugar mg.%		72	66		101	97	101	94	96	67	84		53
	15 Min.		48	60		61	110	84	53	86	67	61		26
	30 "		40	42		58	72	78	43	73	31	33		24
	45 "		42	55		48	81	40	17	60	48	42		38
	60 "		67			23	67	53	28	59	28	33		42
	90 "		63			63	78	58	35	67	50	63		
	120 "		94	*		81	84	58		73	26	72		*
	Absolute Eos./cmm.	75–300	163	76	6	6	206	28	219	178	75	109	116	247
	4 Hour Decrease—%	At least 50%	40	18			24		40	17	8	40	46	32
	N-Hormones													
	17-ketos. mg./24 hours	7.5 to 15	5.0	7.4	5.0	3.6	4.5	2.6	3.8		1.9	2.7	1.7	6.5
	Estrogens—M.U.	13–133 (females)	13	133	67	<13	<13	<13			44	<13	<13	
	Gonadotropins—M.U.	13–96 (females)	107		74	29	>125	>125			33		<13	
	Hemoglobin—gm%	15.6 *			10.6	9.9	6.4	10.8	11.6	11.3	8.0	9.9	8.6	
	WBC/cmm	6000–8000			5950	4450	4500	6000	9000	8100	10,000	7700	5700	6600
	Neuts.—%	60–80	54		59	46	62	64	35	55	49		53	39
	Lymphs.—%	20–35	44		35	46	25	33	59	42	48		40	52

* Test terminated because of severe hypoglycemic symptoms.

was ascertained by determination of urinary 17-ketosteroid; urinary estrogens and gonadotropins are also being reported for reasons which will become apparent. The I_{131} uptake by the thyroid gland was measured by the method of Lasche *et al.*[11].

The results of these studies as well as the values considered normal in this laboratory are listed in Table 1.

Discussion. It is evident from these data that adrenal cortical function is diffusely depressed in all these patients, although electrolyte changes are least marked. This latter finding is not surprising in view of the severe cortical involvement which is necessary before variations in serum electrolyte levels become manifest. Of greater interest is the finding of decreased adrenal cortical function in those patients considered by the Authors to be primary thyroid myxedema. It might be argued that they are in fact instances of pituitary myxedema, but it seems statistically improbable that 12 such patients would appear consecutively in the Endocrine Clinic. Furthermore, patient F. G., Case 1, became myxedematous after thyroidectomy, and patient C. G., Case 2 was myxedematous on the basis of methyl thiouracil overdosage and could not represent primary pituitary failure.

Means[12] suggests that low gonadotropins in the presence of amenorrhea is evidence in favor of the diagnosis of pituitary myxedema, but that normal or elevated gonadotropins are found in thyroid myxedema. This would appear to be the case in these patients and is further evidence of the accuracy of our clinical impressions.

In all but 3 patients, fasting eosinophil levels were normal although the response to hypoglycemic stress was diminished. Patients 1 (W. B.), 2 (C. M.), and 4 (P. K.), showed eosinophil counts ranging from 6 to 28 cells per cmm. on repeated determinations. The reasons for this are not clear unless it represents a direct bone marrow effect. Lymphocyte percentages were generally elevated, as would be expected in deficiency of the adrenal cortex. The significance of an initial elevated serum cholesterol in the differential diagnosis of myxedema is as yet obscure.

Further attempts at a differential diagnosis, by assaying the effect of thyrotropic hormone on the radio-active iodine uptake of the thyroid gland, and also by measuring tolerance to desiccated thyroid, are now under way and will be the subject of another report. However, it is already evident that certain of the patients diagnosed as primary thyroid myxedema in this paper do in fact appear to fit this diagnosis.

It appears that a more likely explanation for these findings is that the pituitary and adrenal glands share in the myxedematous changes that are consequent to the hypothyroidism. As a result of direct effect upon the adrenal, or perhaps secondarily to the pituitary involvement, or even because of a combination of both these factors, adrenal cortical deficiency develops. Some evidence is available to substantiate such a point of view. Hurxthal[9], Benda and Bixby[1] and others, have noted enlargement of the sella turcica in cretins and in experimental thyroidectomy. Benda[1] has reported that the acini of the anterior pituitary glands are infiltrated with albuminous fluid progressing to cystic degeneration. Deane and Greep[4] have shown a decrease in the size of the adrenal cortex with a depletion of its steroid content in experimentally induced hypothyroidism. Vieillard and Perloff[17] noted a decreased eosinophil response to stress in thyroidectomized rats. Many reports of decreased urinary excretion of 17-ketosteroids[5,7], and 11-

oxysteroids[3,14], in myxedematous patients are available. It may well be that the abnormalities of pigmentation so often seen in thyroid disorders are on an adrenal basis.

If this hypothesis is valid, then involvement of the adrenal cortex in myxedema cannot be employed as a method of differentiating primary thyroid from pituitary myxedema, and statistics will have to be adjusted accordingly.

The response to thyroid medication in these patients has been interesting. In no instance where hypertension existed did the blood pressure rise, although it was noted to fall in some patients. Case 7 (A. H.) who suffered with angina was markedly relieved from this symptom with 2 gr. of U.S.P. thyroid daily. Kern and Soloff[10] reported pericardial effusion in their patients with myxedema. When effusion was present in our patients, it disappeared promptly with thyroid medication. Elevated cholesterols consistently dropped to normal levels on adequate thyroid dosage.

Summary. Data have been accumulated in 12 patients with myxedema, which tend to show that the adrenal cortex is adversely affected in primary myxedema so that its functions are depressed. Since this functional depression has been the basis on which the differentiation between pituitary and thyroid myxedema has been made, it is suggested that reports of pituitary myxedema in the literature may be erroneous.

It is believed that the myxedematous changes incident to the primary hypothyroidism involve the adrenal either directly, or secondarily through the pituitary gland, or possibly by a combination of both these factors.

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REFERENCES

1. **Benda, C. E.**, and **Bixby, E. M.**: J. Clin. Endocrin., **7**, 503, 1947.
2. **Daughaday, W. H., Jaffe, H.**, and **Williams, R. H.**: Ibid., **8**, 166, 1948.
3. Idem: Ibid., **8**, 244, 1948.
4. **Deane, H. W.**, and **Greep, R. O.**: Endocrinology, **41**, 243, 1947.
5. **Engstrom, W. W.**, and **Mason, H. L.**: J. Clin. Endocrin., **4**, 517, 1944.
6. **Fraser, R. W., Albright, F.**, and **Smith, P. H.**: Ibid., **1**, 297, 1941.
7. **Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H.**, and **Reinfenstein, E. C., Jr.**: Ibid., **1**, 234, 1941.
8. **Hanneman, P. H., Wexler, H.**, and **Westenhaver, M. H.**: J. Lab. and Clin. Med., 34, 1017, 1949.
9. **Hurxthal, L. M.**: Med. Clin. No. Am., Jan., p. 122, 1947.
10. **Kern, R.**, and **Soloff, L.**: Trans. Assn. Am. Phys., **61**, 158, 1948; idem: Am. J. Med. Sci., **217**, 608, 1949.
11. **Lasché, E. M., Schneeberg, N. G., Perloff, W. H., Serber, W., Sopp, T. E.**, and **Stanton, L.**: J. Phila. Gen. Hosp., **1**, 13, 1950.
12. **Means, J. H., Hertz, S.**, and **Lerman, J.**: Trans. Assoc. Am. Phys., **55**, 32, 1940.
13. **Robinson, F. J., Power, M. H.**, and **Kepler, E. J.**: Proc. Staff Meet. Mayo Clin., **16**, 577, 1941.
14. **Talbot, N. B., Albright, F., Saltzman, A. H., Zygmuntowicz, A.**, and **Wixom, R.**: J. Clin. Endocrin., **7**, 331, 1947.
15. **Thorn, G. W., Forsham, P. H. Prunty, F. T. G.**, and **Hills, A. G.**: J. Am. Med. Assn., **137**, 1005, 1948.
16. **Tucker, H. St. G., Jr., Chitwood, J. L.**, and **Parker, C. P., Jr.**: Ann. Int. Med., **32**, 5[illegible], 1950.
17. **Vieillard, C.**, and **Perloff, W. H.**: Unpublished data.

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TREATMENT OF THE PATIENT WITH HYPERTHYROIDISM

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A FEW years ago the only satisfactory method of handling the patient with hyperthyroidism was by operation. Recently, however, both the thiourea derivatives and radio-active iodine have been used successfully in the treatment of toxic goiter. The purpose of this paper is to attempt to deduce from the very extensive and sometimes confusing mass of literature available a reasonable plan for the management of patients with hyperthyroidism.

HISTORICAL. Early in the 19th century, Graves and Basedow independently presented excellent accounts of the clinical picture of diffuse toxic goiter. Shortly thereafter it became evident that certain patients with this disease were benefited when given iodides by mouth. Unfortunately the improvement resulting from iodine therapy was often short lived, and its use as sole therapy was therefore never widely accepted.

Toward the close of the last century, Kocher developed and popularized the operation of partial thyroidectomy. By 1912 he had performed 5000 such operations with a mortality of less than 5%[14]. Most of his patients, however, had non-toxic goiter, and the operative mortality for those with hyperthyroidism was considerable. Because of this high operative risk, other more satisfactory methods of treatment were sought. Roentgen-ray therapy to the thyroid region was one such possibility. It was used rather extensively early in the present century, but the results were only fair, recurrences were com-

mon and subsequent operation was made more difficult by the radiation fibrosis which always occurred. Yet sporadic use of irradiation to the thyroid continued until 1923. In that year, Plummer[141] showed that preoperative use of iodine in the hyperthyroid patient transformed a dangerous operation into a relatively safe one. Plummer's work quickly won wide acceptance and it soon became apparent that not only the immediate but also the long term results of operation were superior to any previous method of approach. Therefore, Roentgen-ray therapy was abandoned in general and subtotal thyroidectomy became the standard treatment for hyperthyroidism.

As experience with iodine and thyroidectomy accumulated, other fundamental measures in the preoperative control of the patient with hyperthyroidism gradually were established. These were found to include adequate rest with sedation, a high caloric, high protein, high carbohydrate diet with supplemental vitamins, and added calcium and phosphorus. It has been emphasized frequently that, whatever form of therapy one prefers today, these latter measures remain of great importance in the general care of patients with hyperthyroidism.

General Considerations. A prerequisite to the adequate management of hyperthyroidism is a working knowledge of the histology, chemistry and physiology of the thyroid gland. During recent years the use of goitrogenic substances and radioiodine in thyroid research has resulted in remarkable advances. Outstanding among the reports[38,43,70,71,103,104,149,151,160,164,168,169,182] of this progress is a Symposium: "Thyroid Function as Disclosed by Newer Methods of Study"[126], which describes in detail many important recent contributions. It must be admitted, however, that studies concerning the etiology of hyperthyroidism[78,127] have thus far been unproductive of tangible results.

Despite the newer methods in thyroid study the diagnosis of thyroid disease still rests on the clinician's appraisal of all available data[116]. In addition to the basal metabolic rate[12], the determination of protein-bound iodine[33,158,159], which appears to be a direct measure of circulating thyroid hormone, is finding favor in several clinics. Where facilities are available, radioiodine tracer doses may be administered and thyroid function estimated by direct Geiger count[86,133,135,173,174] (the generally preferred method), by excretion studies[56,86] or by the more elaborate and possibly more accurate method of thyroid clearance[85,134]. Such radiation appraisals of thyroid function are possible because the animal and human organisms are incapable of differentiating between stable iodine and its several radioactive isotopes. Radioactive iodine and its importance in the diagnosis and treatment of hyperthyroidism will now be considered in greater detail.

Radioactive Iodine. A number of radioactive isotopes of iodine have been identified and at least 4 of them have been used in biological work. Until recently, these isotopes were prepared in small amounts in the cyclotron[25,84], and were therefore not generally available. For some time however the Atomic Energy Commission, through the Oak Ridge National Laboratories, has been able to supply physicians throughout the country with any desired amount of I^{131} [111]. This isotope, which has a half-life of 8 days, is very suitable for biological work, and is thus the only one in general use at the present time. I^{131} is produced in the uranium chain-reacting pile[111]; it disintegrates to xenon with the emission of a negative beta particle and 2 gamma radiations.

When radioiodine is ingested, 75%

is absorbed from the gastrointestinal tract within 1 hour and the dose is completely absorbed within 3 hours. The thyroid will then concentrate this absorbed iodine up to 10,000 times the blood level, probably at the rate of about 2 to 4% of the total iodide available per hour[86], so that most of the ingested iodine is quickly deposited in the thyroid gland. It does not remain there, however, and about 60 to 70% of the ingested dose will be excreted in the urine in 48 hours if kidney function is normal.

Diagnostic Uses. In hyperthyroidism, small doses of iodine are concentrated in the thyroid more rapidly than in normal persons and the rate of urinary excretion is diminished to a corresponding degree. The diagnostic value of these variations in iodine uptake and excretion is being studied at the present time. As already mentioned, urinary excretion studies[56,86] and estimations of the rate at which the thyroid removes iodide from the blood—thyroid clearance[85,134]—are being done and are perhaps the most accurate methods of study. It appears, however, that direct Geiger-Mueller counter estimations of thyroidal radioiodine uptake are sufficiently accurate for clinical purposes and thus of more practical significance[86,133,135,173,174].

If a tracer dose of I^{131} (30 to 100 microcuries) be given by mouth, its uptake by the thyroid is readily determined because the gamma radiations pass through the tissues without damaging them significantly and can be quantitatively recorded by a Geiger counter placed over the thyroid gland. At the same time, the beta particles arising from the disintegration of I^{131} as far as is known have no appreciable damaging effect on tissues in these doses.

The normal range of uptake, which has been measured by a Geiger counter placed a standard distance (15 cm.) directly in front of the thyroid 24 hours after ingestion of a tracer dose, is between 10 and 40%. In hyperthyroidism this figure will be increased. Werner *et al.*[173] feel that this diagnostic use of radioiodine may prove superior to the BMR in evaluation of thyrotoxicosis, but it must be pointed out that there is an overlap of some 10% between euthyroid and thyrotoxic groups, that the test requires 24 hours to complete and that elaborate precautions and equipment must be used. Great care also must be taken to be sure that the patient has not taken any iodine, goitrogens, thiocyanates or gallbladder dye by mouth prior to the test. Furthermore it appears that diseases other than hyperthyroidism, such as cardiac decompensation, may give misleading or equivocal results.

Therefore the value of tracer studies in the diagnosis of hyperthyroidism is not well established at the present time. The method may be of considerable value in those cases where the diagnosis of hyperthyroidism remains questionable after repeated BMR determinations have been done, but further experience must accumulate before it can be generally recommended for routine diagnostic use.

Therapeutic Uses. The beta particle or electron given up by I^{131} in its disintegration travels only 1 or 2 mm. in tissue but has an extremely intense ionizing effect throughout this range and therefore will destroy tissue cells if concentrated within them in adequate amounts. In the tracer doses mentioned above, the amounts are too small for this effect, but if larger doses are given, for example 5 to 10 millicuries (1 millicurie = 1000 microcuries), the isotope will be concentrated in the thyroid gland and will destroy many of the cells within which it is deposited. Since the hyperactive acini take up most of the radioiodine, as can be shown by radio-autography[69], a

highly selective and efficient method of irradiation control of thyrotoxicosis should be available in this method.

Within certain limits this has proved to be true. A sufficient number of patients now has been treated at several clinics in this country to indicate the usefulness of the method and some of its limitations[14,27,36,59,64,67,69,72,73,80,117,125,136,140,142,155,156,177]. Dosage is still uncertain. The amount required for any individual case of hyperthyroidism is based on the severity of the toxicity and the estimated weight of the thyroid gland[67]. An average initial dose of 4 to 8 millicuries of I^{131} may be given, and smaller doses repeated later if necessary. The total dosage required to control the hyperthyroidism has varied from 2 to 20 millicuries.

The clinical response to radioiodine frequently takes the following pattern[155]: in 1 to 3 days the gland becomes tender, sedimentation rate increases, and in 4 to 10 days there is an augmentation of toxicity. If these events do not occur, the treatment is likely to fail. Clinical improvement may be apparent in 12 to 14 days, but the optimal effect does not occur until 6 to 8 weeks have elapsed. At the end of that time, further treatment may be undertaken if remission is not complete. In 1 month 97% of the radioactivity is dissipated.

The effect of radioiodine on the architecture of the thyroid has been studied by biopsy of the gland. One investigator[59] states that there is no characteristic pattern in the reaction to radiation, while another[27] points out that there is fibrosis and decrease in the number of follicles, but that the remaining follicles continue to show hyperplasia, indicating that the original stimulation which produced the hyperthyroidism still is present.

Results. There have now been reported in the literature more than 300 cases of hyperthyroidism treated with radioiodine[27,67,72,73,117,125,142,155,156]. A review of these reports indicates that about two-thirds of the patients are clinically cured. Most of the remainder have improved, and it is assumed that they will be cured following further therapy.

The goiter has invariably become smaller in cases treated successfully, and in a considerable percentage has disappeared completely. There has been no damage to adjacent structures in the neck such as the parathyroids and recurrent nerves. Myxedema was produced in 19 patients, transient exacerbation of thyrotoxicosis was seen occasionally, slight to moderate increase in exophthalmos occurred in a considerable number of patients, and mild radiation sickness was seen in a few patients. There were only 6 frank failures of the treatment.

The advantages of radioiodine over other methods of treatment of hyperthyroidism have been summarized by several investigators[27,67,72,73,142,155] as follows: 1. The material is given as a single dose of a colorless, odorless, tasteless material. It is taken by mouth in a small glass of water by the ambulant patient without the necessity for frequent follow-ups or laboratory work.

2. No fatalities have been directly attributable to the treatment.

3. Radiation sickness is infrequent.

4. All the disadvantages of operation—mortality, morbidity, cost, and post-operative complications — have been eliminated completely.

On the other hand the present disadvantages are not inconsiderable—

1. The correct dosage has not yet been established.

2. Considerable technical skill and apparatus, with adequate protection of personnel, are required[136].

3. The cytological diagnosis remains

unconfirmed unless the thyroid gland is biopsied.

4. Other types of radiation therapy of hyperthyroidism have given poor results.

5. The material has been in use a relatively short period of time; there may be unknown dangers, such as carcinogenesis, tumor formation, hypophyseal change, or kidney damage, which may not appear until after many years have elapsed.

Because of these disadvantages many workers at present prefer to use radioactive iodine for the treatment of hyperthyroidism only in those patients who are 50 years of age or over and who have diffusely enlarged glands, or in those who refuse operation. In addition, there may be included carefully selected cases of recurrent post-operative hyperthyroidism[45] and certain problem cases of thyrotoxicosis which fail to respond to antithyroid drugs or are refractory to other more standarized forms of treatment.

Antithyroid Drugs. The initial stimulus for the study of antithyroid materials occurred in 1928 with the work of Chesney, Clawson and Webster[28] who reported the production of hyperplastic goiters and lowered metabolism in a colony of rats used in the study of syphilis and fed a diet of cabbage. Similar important early studies on this problem were conducted by McCarrison[113,114,115] in India. Subsequently 4 different groups of goitrogens were identified: the cyanides[112], thiocyanates[8], certain aniline derivatives related to the sulfonamides[108], and thiourea and its derivatives[88,147]. Astwood[5] first reported the clinical use of thiourea and thiouracil in 1943. In 1946, with VanderLaan, he[7] reported his experiences with the less toxic propylthiouracil. Methylthiouracil has been employed extensively in Europe[20, 29,60,107,128] and by some in this country[10,120]. Aminothiazole has been used in France[10] and thiobarbital received a brief trial but because of the high incidence of reactions was abandoned. A large number of other compounds have been investigated in the laboratory and currently iodothiouracil[179] is undergoing clinical evaluation, but thus far none is superior to either propylthiouracil or methylthiouracil.

The thiourea derivatives are therapeutically effective by interfering with the synthesis of thyroxin by the thyroid gland[41,44,54,55,101,102,139,145]. This results in a decrease of normal inhibition of the anterior pituitary by the thyroid, thus permitting augmented secretion of thyrotropin (TSH).

The action of iodine in controlling hyperthyroidism on the other hand, may occur in 2 ways. There is evidence that iodine inactivates TSH[14,39] and thus reduces the stimulation of the thyroid. Secondly, there is a homeostatic mechanism in which elevation of the plasma iodine above 20 to 35 micrograms per 100 cc. blocks organic binding of iodine in the thyroid even though there is a surplus of iodine accumulated in the gland[42,180,181,182].

For these reasons some investigators[14,120] are prescribing Lugol's solution throughout therapy with antithyroid substances, or, at least, initiating the treatment with iodine and then employing it again immediately before operation. It has also been reported that iodine is more effective if a thiourea derivative has been used previously[21].

Propylthiouracil. The greatest clinical experience has been with propylthiouracil[4,10,14,36,116, 120,123,140,146,157, 178,182] and with this drug the optimum dosage appears to be about 200 to 300 mg. daily in divided doses at 8 hour intervals. If medical management is mandatory it is advisable to continue

this dosage until the euthyroid state has been maintained for 6 to 12 months or until hypothyroidism supervenes. In preparation for surgery, the proper time for thyroidectomy must be decided on clinical grounds rather than by dependence upon laboratory procedures.

The results of treatment with propylthiouracil are ideal when it is used preoperatively. On the other hand, attempts to obtain sustained remissions with prolonged medical therapy often fail[80] either because the patients become restive during the necessarily prolonged treatment or because relapses occur when the drug is stopped. The wide variation in reported sustained remissions on propylthiouracil treatment alone[14,15,20,116,146,153,157] may be explained by the failure to include in the more successful series the severely toxic and those patients who were lost on the prolonged medical regimen. With a few notable exceptions[157] the general opinion is that slightly less than half of the mildly thyrotoxic patients with small goiters may be controlled with propylthiouracil, but no series of cases has been followed long enough to know whether late recurrences may appear even in this selected group. Conversely it is believed that all severely toxic patients, those with nodular goiters (particularly solitary adenomas) and those with large toxic diffuse goiters, should be carefully and expeditiously prepared with propylthiouracil or methylthiouracil and have thyroidectomies unless there are other contraindications to surgery.

Undesirable Effects of Propylthiouracil. These include toxic effects, changes in exophthalmos, and increasing size of the thyroid gland.

(a) *Toxic effects.* The only important toxic effects of the drug are granulocytopenia[9] and drug fever. Leukopenia[50] is relatively common in thyrotoxicosis and therefore only when the total white count drops below 4000 and the granulocytes below 30% does it become necessary to stop treatment. Even then, very cautious readministration may be undertaken with frequent blood counts. Otherwise it is seldom necessary to have counts done more often than once a month after initial studies. Patients, however, must be cautioned to report immediately if sore throat, fever, skin eruption, lymphadenopathy or malaise occur. The use of propylthiouracil following the previous use of thiouracil[163] may induce agranulocytosis and there has been one fatality in a patient with interrupted therapy[83]. Apparently reinstitution of treatment demands close observation. Other problems which have been encountered[9,50,65,97,100,106,118,122,172] are hepatocellular jaundice, skin eruptions, edema, sialadenitis and pancreatitis. In experimental studies on rats, parathyroid hyperplasia occurred in about one-fourth of the animals when propylthiouracil therapy was continued longer than 14 months[110]. Tumor production also has been noted following prolonged administration of the antithyroid drugs to these laboratory animals, but has not been observed in humans[17,19,77,129,143].

(b) *Increasing exophthalmos.* Contary to previous opinion[3,13,37,47,63,119,154] recent experimental work[82] suggests that the anterior pituitary thyrotropic hormone per se does not produce exophthalmos and that thyroidectomy does not aggravate exophthalmos. The authors' clinical experience is in accord with this idea. For there has been a consistent increase in exophthalmos during propylthiouracil therapy in a significant number of cases, and no further increase or an actual decrease has been observed following thyroidectomy[163]. If, as Jefferies[82] believes, exophthalmos is not co-

trolled by the thyrotropic hormone but is under the influence of another anterior pituitary factor, it is not quite clear why thyroidectomy tends to check the progression of exophthalmos. In any event it has been of value to observe patients carefully for evidence of increasing exophthalmos while on propylthiouracil, and, when it occurs, to undertake thyroidectomy at the earliest possible time following adequate preoperative preparation. The results of operation have proved to be very encouraging[163] despite reports of others[47,119,154] that exophthalmos usually increases following thyroidectomy.

(c) *Increasing size of goiter.* The goitrogenic effect of the thiourea derivatives was one of the first observations made in the experimental study of these drugs[6,88]. Clinically, this goitrogenic effect is seldom observed, but when it does occur, operation should be performed as soon as the BMR can be brought down to normal. We have recently taken care of 2 patients who had a tremendous increase in the size of the thyroid while on propylthiouracil, and who were at the same time resistant to its antithyroid effects, so that doses up to 900 mg. daily failed to lower the BMR. One of these patients was given radioiodine to control the thyrotoxicosis and subsequently was operated upon successfully[162]. Studies suggesting that estrogens[61] and bismuth salts[171] may control the size of the thyroid under these circumstances have not been verified.

THYROIDECTOMY. Although Kocher[16, 89] was the real pioneer in thyroid surgery, many others have contributed to its development. Shortly after the turn of the century, Halsted[68] reported a technique for subtotal thyroidectomy which differs little from the operation performed today. Crile[34,35], Lahey[90,91, 92,93,95,99] and others[23,30,46,66,76,109,150] have further perfected the procedure so that complications such as recurrent nerve paralysis, hemorrhage and parathyroid tetany seldom are observed after operation[94]. Post-operative recurrence of hyperthyroidism as a rule is due to removal of an inadequate amount of the thyroid gland, and does not often occur. Extirpation of the entire isthmus and of all but a small shell of the posterior part of each lateral lobe will result in a low recurrence rate, usually around 5%[79]. The occasional case of post-operative hypothyroidism is easily managed by the administration of dessicated thyroid. Hertzler[74] and Scott[152] have advocated total thyroidectomy in all cases of toxic goiter, but other authorities agree that total thyroidectomy invariably results in myxedema.

Technical advances in recent years have not been of great significance. Lahey[93,99] prefers to divide the prethyroid muscles for adequate exposure and he attempts to visualize and protect the recurrent nerves in every thyroid operation. Others[46,76,109,150] feel that these measures and precautions are not necessary.

Prior to 1943 thyroidectomy for toxic goiter carried a mortality of from 1 to 4% in good hands[32,75,91], even though multiple stage operations were performed in the poor risk cases[165]. This is explained on the basis that preoperative iodine therapy was effective only for a matter of a few weeks during which time many patients could not be brought sufficiently under control for safe operation.

The antithyroid drugs have changed this picture completely. Propylthiouracil will convert the severely toxic patient to a non-toxic patient[98], and can be used for any desired length of time, so that cardiac or other complications may be more readily controlled. Operation for toxic goiter, thus, at long last becomes a truly elective procedure and the operative mortality has decreased to an almost irreducible mini-

mum, certainly less than 1%[10,23,24,62]. In a recent small series of our own cases[163] there were no operative deaths. Post-operative thyroid storm has been eliminated and multiple stage operations are no longer necessary.

Since the thiourea derivatives cause further hyperplasia of the thyroid, producing a soft, friable, bleeding gland, iodine is given, as it has been in the past, to involute the gland preoperatively. We agree with others[96,98,100] that it should be given for at least 3 weeks before operation. After this time the operation is usually easy technically because the gland is firm and less vascular.

Anesthesia. Individual preferences for anesthesia in thyroidectomies vary considerably, but all agree that the maintenance of a clear airway to insure an adequate continuous supply of oxygen is of the greatest importance in operations on the hyperthyroid patient[2,15,51,52,130]. Our personal feeling is that this is most satisfactorily accomplished by the use of general anesthesia with tracheal intubation. The following technique, which has been outlined by Dr. Ivan Taylor of the department of Anesthesia at the Wayne University College of Medicine[161], has been found very satisfactory. Induction is performed with pentothal sodium and curare supplemented by topical anesthesia of the larynx. Intubation of the trachea is then done and is followed by nitrous oxide-oxygen anesthesia. Recently, continuous intravenous drip of 1% procaine hydrochloride at a rate of about 40 mg. (4 cc.) per minute also has been used. The procaine is only an adjunct but supplements the anesthesia enough to permit completion of the operation with nitrous oxide and oxygen. In addition, the procaine seems to depress the cough reflex, gives analgesia for from 30 minutes to several hours post-operatively, and keeps the patient quiet with no retching or excitement. Thus, with this technique one can expect rapid recovery from the nitrous oxide, so that patients are usually mentally clear in 5 to 15 minutes after operation but do not experience any pain for several hours.

Psychotherapy of Thyrotoxicosis. Although psychotherapy of thyrotoxicosis has been attempted from time to time, there are no recent convincing reports of success in this field. With regard to etiology, it is said that no authenticated case of hyperthyroidism occurring during World War II was directly related to psychic trauma[48]. This idea is at variance with the previously held opinion[124] that psychic factors were important in the pathogenesis of thyrotoxicosis. Whichever view is correct, it seems reasonable to recognize the fact that hyperthyroid patients do present certain psychosomatic problems[131] and that these problems merit careful consideration and appropriate treatment.

Circumscribed Myxedema. Myxedema circumscriptum thyrotoxicum has recently been studied in some detail[31,37,58,105,167,170]. The occurrence of localized myxedema, usually on the anterolateral surface of the legs, has been reported in 3% of one series of 130 cases of hyperthyroidism[167]. It is said to occur as a rule following thyroidectomy and it is often associated with progressive exophthalmos. The augmented secretion of anterior pituitary thyrotropic hormone following removal of the inhibitory mechanism by thyroidectomy is proposed by some as the cause of both conditions[37]. Treatment, which is not very satisfactory, has included desiccated thyroid, Lugol's solution, and estrogens.

Thyrotoxicosis in Pregnancy. The management of hyperthyroidism in the gravid patient has been well summarized by Means, who has stated that it is the thyrotoxicosis and not the pregnancy which should be interrupted[124].

Since the fetal thyroid begins to develop and becomes functional at about the 14th week of pregnancy it would seem wise to avoid the use of antithyroid drugs and radioiodine after that time, since both substances are capable of passing the placental barrier[26,132]. However, several investigators[1,7,49,121,138,148,176] have continued such therapy throughout pregnancy. No ill effects were reported in one infant followed for 16 months after the use of propylthiouracil[22] nor in another followed for 18 months after radioiodine was given to the mother[26]. On the other hand histological studies of fetal thyroid following the administration of thiourea derivatives to the mother have shown hyperplastic acini which look much like the picture of Grave's disease in the adult[40,57].

Until further and more complete studies of these effects are available, it would seem wise to treat the hyperthyroid pregnant patient with iodine and subtotal thyroidectomy.

THYROTOXICOSIS IN CHILDREN. Hyperthyroidism is rare in children and extremely rare in boys[11,18,53,175], but when it does occur, is a serious and dangerous disease. Because of this, Topper[166] prefers to treat such cases medically, using iodine, rest, sedation and vitamins. She reports 6 of 8 patients so treated cured, 1 lost to follow up and 1 dead of unrelated causes. Olesen and Schiodt also prefer medical therapy[137]. Other workers, including Bartels[11], Jackson[81], Crile[36] and Kennedy[87] report excellent results following operation, and point out that careful preoperative preparation with propylthiouracil has reduced the surgical risk to a very low figure, just as it has done in the adult.

Conclusions. The current literature on the treatment of hyperthyroidism has been reviewed in an effort to assess the value of newer methods of therapy, particularly propylthiouracil and radioactive iodine. The following conclusions are based partly on this review and partly on the personal experience of the authors.

1. Subtotal thyroidectomy remains the treatment of choice for patients suffering from hyperthyroidism.

2. Mild cases may be prepared satisfactorily with iodine for 10 days to 2 weeks preceding operation.

3. Severely toxic patients and those with complications should be treated with propylthiouracil long enough to eliminate toxicity or to permit satisfactory control of complications. Iodine then may be given for 3 weeks and operation performed with no greater risk than in the initially mild cases.

4. Non-operative treatment of hyperthyroidism is still undergoing evaluation.

(a) Prolonged treatment with antithyroid drugs is rarely justifiable. The mildly toxic patient with a small diffusely enlarged thyroid may be treated in this way but the chance of permanent cure is small.

(b) Radioactive iodine offers great promise in the treatment of hyperthyroidism, but until the dosage can be estimated more accurately, and until the problem of late deleterious effects has been resolved, this method of treatment should be limited to patients of advanced age or others in whom surgery is contraindicated.

These concepts are in accord with those of Ravdin, Rose and Maxwell[144] who have had an extensive personal experience in dealing with hyperthyroid patients.

Finally, it must be emphasized that there is no truly physiological treatment for hyperthyroidism available today. However, the search for such a rational form of therapy must continue and the newer methods of study of thyroid function and disease make probable its eventual discovery.

REFERENCES

(1) **Acton, W. C.,** and **Cottrell, J. D.:** Canad. Med. Assn J., **61,** 27, 1949. (2) **Adams, R. C.,** and **Dixon, C. F.:** Surgery, **16,** 700, 1944. (3) **Adler, F. H., Scheie, H. G.,** and **Dennis, R.:** J. Mich. State Med. Soc., **48,** 852, 1949. (4) **Anglem, T. J.,** and **Kenney, F. R.:** Am. J. Surg., **78,** 210, 1949. (5) **Astwood, E. B.:** J. Am. Med. Assn., **122,** 78, 1943. (6) **Astwood, E. B., Sullivan, J., Bissell, A.,** and **Tyslowitz, R.:** Endocrinology, **32,** 210, 1943. (7) **Astwood, E. B.,** and **VanderLaan, W. P.:** Ann. Int. Med., **25,** 813, 1946.

(8) **Barker, M. H.:** J. Am. Med. Assn., **106,** 762, 1936. (9) **Bartels, E. C.:** Am. J. Med., **5,** 48, 1948. (10) Idem: J. Clin. Endocrin., **8,** 766, 1948. (11) Idem: Lahey Clinic Bull., **6,** 68, 1949. (12) Idem: J. Clin. Endocrin., **9,** 1190, 1949. (13) **Beierwaltes, W. H.:** Arch. Int. Med., **81,** 364, 1948. (14) **Beierwaltes, W. H.,** and **Sturgis, C. C.:** Med. Clin. No. Am., **33,** 497, 1949. (15) **Benitez, J. N., Raffucci, F. L.,** and **Giusti, J. R. G.:** Puerto Rico J. Pub. Health and Trop. Med., **25,** 1, 1949. (16) **Bett, W. R.:** Med. Bookman and Historian, **1,** 29, 1947. (17) **Bielschowsky, F.:** Brit. J. Exp. Path., **25,** 1, 1944. (18) **Bram, I.:** Arch. Ped., **54,** 419, 1937. (19) **Broders, A. C.,** and **Parkhill, E. M.:** Surgery, **16,** 633, 1944. (20) **Brull, L.,** and **Lefebvre, L.:** Revue Médicale de Liège, **3,** 357, 1948. (21) **Buno, W.,** and **Grosso, F. O.:** Arch. Path., **48,** 27, 1949.

(22) **Caren, R.:** J. Clin. Endocrin., **9,** 903, 1949. (23) **Cattell, R. B.:** West. J. Surg., **56,** 77, 1948. (24) **Cattell, R. B.:** J. Clin. Endocrin., **9,** 999, 1949. (25) **Chaikoff, I. L.,** and **Taurog, A.:** Univ. Wisconsin Press, p. 292, 1948. (26) **Chapman, E. M., Corner, G. W., Jr., Robinson, D.,** and **Evans, R. D.:** J. Clin. Endocrin., **8,** 717, 1948. (27) **Chapman, E. M.,** and **Evans, R. D.:** J. Am. Med. Assn. **131,** 86, 1946. (28) **Chesney, A. M., Clawson, T. A.,** and **Webster, B.:** Bull. Johns Hopkins Hosp., **43,** 261, 1928. (29) **Clark, W. E.:** Brit. Med. J., **1,** 597, 1948. (30) **Clute, H. M., Kennedy, F. R.,** and **Hamilton, B. E.:** Surgery, **16,** 739, 1944. (31) **Cohen, E. L.:** Brit. J. Dermatol., **58,** 173, 1946. (32) **Cole, W. H.:** Surgery, **16,** 688, 1944. (33) **Connor, A. C., Curtis, G. M.,** and **Swenson, R. E.:** J. Clin Endocrin., **9,** 1185, 1949. (34) **Crile, G.:** Surg., Gyn. and Obst., **67,** 363, 1938. (35) **Crile, G.,** and **Lower, W. E.:** Ibid., **34,** 358, 1922. (36) **Crile, G., Jr.:** Practical Aspects of Thyroid Disease, Philadelphia, W. B. Saunders, 1949. (37) **Curtis, A. C., Cawley, E. P.,** and **Johnwick, E. B.:** Arch Dermatol. and Syphil., **60,** 318, 1949.

(38) **D'Angelo, S. A., Gordon, A. S., Paschkis, K. E.,** and **Cantarow, A.:** J. Clin. Endocrin., **9,** 653, 1949. (39) **Danowski, T. S., Man, E. B., Elkinton, J. P., Peters, J. R.,** and **Winkle, A. W.:** Am. J. Med. Sci., **215,** 123, 1948. (40) **Davis, L. J.,** and **Forbes, W.:** Lancet, **2,** 740, 1945. (41) **Dempsey, E. W.:** Endocrinology, **34,** 27, 1944. (42) **DeRobertis, E.:** West. J. Surg., Obst. and Gyn., **56,** 253, 1948. (43) Idem: J. Clin. Endocrin., **8,** 956, 1948. (44) **DeRobertis, E.,** and **Grasso, R.:** Endocrinology, **38,** 137, 1946. (45) **Dinsmore, R. S.,** and **Schneider, R. W.:** Surg. Clin. No. Am., **29,** 1329, 1949. (46) **Dixon, C. F.:** Ibid., **23,** 1083, 1943. (47) **Dobyns, B. M.,** and **Haines, S. F.:** J. Clin. Endocrin., **6,** 633, 1946. (48) **Dynes, J. B.:** Lahey Clinic Bull., **6,** 153, 1949.

(49) **Eaton, J. C.:** Lancet, **1,** 171, 1945. (50) **Eisenmenger, W. J.,** and **Steele, J. M.:** J. Am. Med. Assn, **135,** 510, 1947. (51) **Eversole, U. H.:** Trans. Am. Assn Study Goiter (1942-1946), p. 41, 1946.

(52) **Fahrni, G. S.:** Int. Coll. Surg. J., **12,** 414, 1949. (53) **Farquhar, J. W.:** Arch. Dis. in Child., **23,** 259, 1948. (54) **Franklin, A. L., Chaikoff, I. L.,** and **Lerner, S. R.:** J. Biol. Chem., **153,** 151, 1944. (55) **Franklin, A. L., Lerner, S. R.,** and **Chaikoff, I. L.:** Endocrinology, **34,** 265, 1944. (56) **Freedberg, A. S., Buka, R.** and **McManus, M. J.:** J. Clin. Endocrin., **9,** 841, 1949. (57) **Freiosleben, E.,** and **Kjerulf-Jensen, K.:** J. Clin. Endocrin., **7,** 47, 1947. (58) **French, G. N.:** New England J. Med., **241,** 299, 1949. (59) **Friedman, N. B.:** J. Clin. Endocrin., **9,** 874, 1949. (60) **Frisk, A. R.:** Acta Med. Scandinav., **129,** 164, 1947.

(61) **Gassner, F. X., Barrett, H. W.,** and **Gustavson, R. G.:** West. J. Surg., Obst. and Gyn., **56,** 346, 1948. (62) **Goldman, L.:** J. Clin. Endocrin., **8,** 781, 1948. (63) **Goodwin, J. F.:** Brit. Med. J., **1,** 597, 1948. (64) **Gorbman, A.:** Proc. Soc. Exp. Biol. and Med., **71,** 237, 1949. (65) **Grauer, R. C., DeWalt, H., Elkin, C. W. W.:** Am. J. Med. Sci., **215,** 63, 1949. (66) **Guthrie, D.,** and **Schimmel, I.:** Surgery, **16,** 725, 1944.

(67) **Haines, S. F., Keating, F. R., Jr., Power, M. H., Williams, M. M. D.,** and **Kelsey, M. F.:** J. Clin. Endocrin., **8,** 813, 1948. (68) **Halsted, W. S.:** The Operative Story of Goiter, Baltimore, Johns Hopkins Press, 1919. (69) **Hamilton, J. G.,** and **Soley, M. H.:** Am. J. Physiol., **127,** 557, 1939. (70) **Heimer, C. B., Maslow, H. L.,** and **Sobel, A. E.:** J. Nutrition, **38,** 345, 1949. (71) **Hertz, S.,** and **Roberts, A.:** Endocrinology, **29,** 82, 1941. (72) Idem: J. Clin. Invest., **21,** 624, 1942. (73) Idem: J. Am. Med. Assn. **131,** 81, 1946. (74) **Hertzler, A. E.:** Ann. Surg.,

122, 862, 1945. (75) **Heyd, C. G.**: Am. J. Surg., **55**, 18, 1942. (76) Idem: New York State J. Med., **44**, 43, 1944. (77) **Hinton, J. W.**, and **Lord, J. W., Jr.**: J. Am. Med. Assn, **129**, 605, 1945.

(78) **Iversen, K.**: Temporary Rise in Frequency of Thyrotoxicosis in Denmark 1941-1945, Copenhagen, Rosenkilde and Bagger, 1948.

(79) **Jackson, A.**: Trans. Am. Assn. Study Goiter, p. 33, 1946. (80) Idem.: Int. Coll. Surg. J., **11**, 640, 1948. (81) **Jackson, A. S.**, and **Haley, H. B.**: Am. J. Med. Sci., **218**, 493, 1949. (82) **Jefferies, W. M.**: J. Clin. Endocrin., **9**, 927, 1949. (83) **Juliar, B.**, and **Harris, T. L.**: J. Am. Med. Assn, **139**, 646, 1949.

(84) **Kamen, M. D.**: Radioactive Tracers in Biology, New York, Academic Press, 1948. (85) **Keating, F. R., Jr., Wang, J. C., Luellen, T. J., Williams, M. M. D., Power, M. H.**, and **McConahey, W. M.**: J. Clin. Endocrin., **9**, 189, 1949. (86) **Kelsey, M. P., Haines, S. F.**, and **Keating, F. R.**: J. Clin. Endocrin., **9**, 171, 1949. (87) **Kennedy, R. L. J.**: Am. J. Dis. Child. **60**, 677, 1940. (88) **Kennedy, T. H.**: Nature, **150**, 233, 1942. (89) **Kocher, T.**: Textbook of Operative Surgery, Vol. 2, New York, MacMillan, 1911.

(90) **Lahey, F. H.**: Surg., Gyn. and Obst., **66**, 775, 1938. (91) Idem: Ann. Surg., **113**, 730, 1941. (92) Idem: Ibid., **117**, 332, 1943. (93) Idem: Surg., Gyn. and Obst., **78**, 239, 1944. (94) Idem: Surg. Clin. North Am., **24**, 491, 1944. (95) Idem: Surgery, **16**, 705, 1944. (96) Idem: New England J. Med., **236**, 46, 1947. (97) Idem: Bull. U. S. Army Med. Dept., **8**, 294, 1948. (98) Idem: Texas State J. Med., **45**, 25, 1949. (99) Idem: Surg. Clin. No. Am., **29**, 641, 1949. (100) **Lahey, F. H.**, and **Bartels, E. C.**: Ann. Surg., **125**, 572, 1947. (101) **Larson, R. A., Keating, F. R., Jr., Peacock, W.**, and **Rawson, R. W.**: Endocrinology, **36**, 149, 1945. (102) Idem: Ibid., **36**, 160, 1945. (103) **LeBlond, C. P.**, and **Gross, J.**: Endocrinology, **43**, 306, 1948. (104) Idem: J. Clin. Endocrin., **9**, 149, 1949. (105) **Linnell, J. W.**, and **Piercy, J. E.**: Lancet, **257**, 141, 1949. (106) **Livingston, H. J.**, and **Livingston, S. F.**, J. Am. Med. Assn, **135**, 422, 1947. (107) **Lou, H.**, and **Wulff, F.**: Acta Medica Scandin., **133**, 149, 1949.

(108) **Mackenzie, J. B., Mackenzie, C. G.**, and **McCollum, E. V.**: Science, **94**, 518, 1941. (109) **Maes, U., Kuker, L.**, and **Craighead, C.**: Am. J. Surg., **75**, 683, 1948. (110) Malcolm, J., **Griesbach, W. E., Bielschowsky, F.**, and **Hall, W. H.**: Brit. J. Exp. Path., **30**, 17, 1949. (111) Manhattan Project Announcement, Science, **103**, 697, 1946. (112) **Marine, D., Bauman, E. J., Spence, A. W.**, and **Cipra, A.**: Proc. Soc. Exp. Biol. and Med., **29**, 772, 1932. (113) **McCarrison, R.**: Indian. J. Med. Research, **18**, 1311, 1930. (114) Idem: Ibid., **21**, 179, 1933. (115) Idem: Brit. Med. J., **2**, 671, 1933. (116) **McClintock, J. E.**, and **Armstrong, W. G.**: New York State J. Med., **47** (pt. 2), 2597, 1947. (117) **McCullagh, E. P.**: Ohio State Med. J., 46, 127, 1950. (118) **McCullagh, E. P., Hibbs, R. E.**, and **Schneider, R. W.**: Am. J. Med. Sci., **214**, 545, 1947. (119) **McCullagh, E. P., Ruedemann, A. D.**, and **Gardner, W. J.**: Trans. Am. Assn. Study Goiter (1942-1946), p. 15, 1946. (120) **McCullagh, E. P.**, and **Sirridge, W. T.**: J. Clin. Endocrin., **8**, 1051, 1948. (121) **McGavack, T. H.**: Am. J. Med., **5**, 90, 1948. (122) **McGavack, T. H., Gerl, A. J., Vogel, M.**, and **Schwimmer, D.**: J. Clin. Endocrin., **4**, 249, 1944. (123) **McGinty, D. A., Sharp, E. A., Dill, W. A.**, and **Rawson, R. W.**: J. Clin. Endocrin., 8, 1043, 1948. (124) **Means, J. H.**: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott, 2d ed., 1948. (125) **Means, J. H.**: Bull. New York Acad. Med., **24**, 273, 1948. (126) **Means, J. H., et al.**: Ann. New York Acad. Sci., **50**, 279, 1949. (127) **Meulengracht, E.**: Arch. Int. Med., **83**, 119, 1949. (128) **Meulengracht, E.**, and **Kjerulf-Jensen, K.**: J. Clin. Endocrin., **8**, 1060, 1948. (129) **Money, W. L.**: Anat. Rec., **96**, 544, 1946. (130) **Mousel, L. H.**, and **Coakley, C. S.**: Anesthesiology, **10**, 444, 1949. (131) **Musser, M. J.**: Wis. Med. J., **47**, 291, 1948. (132) **Mussey, R. D., Haines, S. F.**, and **Ward, E.**: Am. J. Obst. and Gyn., **55**, 609, 1948. (133) **Myant, N. B., Honour, A. J.**, and **Pochin, E. E.**: Clin. Science, **8**, 135, 1949. (134) **Myant, N. B., Pochin, E. E.**, and **Goldie, E. A. G.**: Ibid., **8**, 109, 1949.

(135) **Nachman, H. M., Crawford, V.**, and **Bigger, I. A.**: J. Am. Med. Assn, **140**, 1154, 1949. (136) **Nickson, J. J.**: J. Clin. Endocrin., **8**, 721, 1948.

(137) **Olesen, K. N.**, and **Schiodt, E.**: Acta Med. Scandinav., (Suppl.) **206**, 278, 1946.

(138) **Palmer, M. V.**: Ann. Int. Med., **22**, 335, 1945. (139) **Paschkis, K. E., Cantarow, A.**, and **Tillson, E. K.**: Proc. Soc. Exp. Biol. and Med., **60**, 148, 1945. (140) **Pemberton, J. deJ., Haines, S. F.**, and **Keating, F. R., Jr.**: J. Clin. Endocrin., **9**, 1232, 1949. (141) **Plummer, H. S.**: J. Am. Med. Assn, **80**, 1955, 1923. (142) **Prinzmetal, M., Agress, C. M., Bergman, H. C.**, and **Simkin, B.**: J. Am. Med. Assn, **140**, 1082, 1949. (143) **Purves, H. D.**, and **Griesbach, W. E.**: Brit. J. Exp. Path., **28**, 46, 1947.

(144) **Ravdin, I. S., Rose, E.**, and **Maxwell, J. D.**: J. Am. Med. Assn, **140**, 141, 1949. (145) **Rawson, R. W., Tannheimer, J. F.**, and **Peacock, W.**: Endocrinology, **34**, 245, 1944. (146) **Reveno, W. S.**: J. Clin. Endocrin., **8**, 866, 1948. (147) **Richter, C. P.**, and **Clisby, K. H.**:

Proc. Soc. Exp. Biol. and Med., **48**, 684, 1941. **(148) Rose, E.,** and **McConnell, J.:** Am. J. Med. Sci., **208**, 561, 1944.

(149) Salter, W. T., and **Johnston, M. W.:** J. Clin. Endocrin., **8**, 911, 1948. **(150) Sanderson, E. R.:** West. J. Surg., **56**, 365, 1948. **(151) Schachner, H., Franklin, A. L.,** and **Chaikoff, I. L.:** J. Biol. Chem., **151**, 191, 1943. **(152) Scott, A. C., Jr.,** and **Ramey, R. M.:** J. Clin. Endocrin., **9**, 1048, 1949. **(153) Sexton, D. L.,** and **Murphy, J. P.:** J. Mo. State Med. Assn, **45**, 22, 1948. **(154) Soley, M. H.:** Arch. Int. Med., **70**, 206, 1942. **(155) Soley, M. H.,** and **Miller, E. R.:** Med. Clin. No. America, **32**, 3, 1948. **(156) Soley, M. H., Miller, E. R.,** and **Foreman, N.:** J. Clin. Endocrin., **9**, 29, 1949. **(157) Starr, P., Pettit, D. W., Meister, L.,** and **Stirrett, R. L.:** J. Clin. Endocrin., **9**, 330, 1949. **(158) Swenson, R. E.,** and **Curtis, G. M.:** Am. Pract., **2**, 671, 1948. **(159)** Idem: J. Clin. Endocrin., **8**, 934, 1948.

(160) Taurog, A., Chaikoff, I. L., and **Feller, D. D.:** J. Biol. Chem., **171**, 189, 1947. **(161) Taylor, Ivan B.:** Personal communication. **(162) Taylor, N.,** and **Large, A.:** Unpublished data. **(163) Taylor, N., Large, A.,** and **Noth, P.:** Am. J. Med. Sci., In press. **(164) Thorek, P.:** Am. J. Surg., **78**, 133, 1949. **(165) Tinker, M. B.,** and **Tinker, M. B., Jr.:** Trans. Am. Assn. Study Goiter, p. 79, 1941. **(106) Topper, A.:** Am. J. Dis. Child., **76**, 26, 1948. **(167) Trotter, W. R.,** and **Eden, K. C.:** Quart. J. Med., **11**, 229, 1942.

(168) VanderLaan, J. F., and **VanderLaan, W. P.:** Endocrinology, **40**, 403, 1947. **(169) VanderLaan, W. P.,** and **Bissell, A.:** Ibid., **39**, 157, 1946. **(170) Vilanova, X.,** and **Canadell, J. M.:** J. Clin. Endocrin., **9**, 883, 1949. **(171) Villaverde, M.:** J. Clin. Endocrin., **9**, 463, 1949.

(172) Welti, H.: La Presse Medicale, **57**, 817, 1949. **(173) Werner, S. C., Goodwin, L. D.,** and **Quimby, E. H.:** J. Clin. Endocrin., **9**, 664, 1949. **(174) Werner, S. C., Quimby, E. H.,** and **Schmidt, C.:** Ibid., **9**, 342, 1949. **(175) Williams, L. P.,** and **Janney, F. R.:** Pediat., **30**, 371,1947. **(176) Williams, R. H.:** J. Clin. Endocrin., **6**, 1, 1946. **(177)** Idem: Arch. Int. Med., **80**, 11, 1947. **(178) Williams, R. H., Asper, S. P., Rogers, W. F., Myers, J. A.,** and **Lloyd, C. W.:** New England J. Med., **236**, 737, 1947. **(179) Williams, R. H., Towery, B. T., Rogers, W. F., Tagnon, R.,** and **Jaffe, H.:** J. Clin. Endocrin., **9**, 801, 1949. **(180) Wolff, J.,** and **Chaikoff, I. L.:** J. Biol. Chem., **172**, 855, 1948. **(181)** Idem: Endocrinology, **42**, 468, 1948. **(182)** Idem: J. Biol. Chem., **174**, 555, 1948.

OPHTHALMOLOGY

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NYSTAGMUS: ITS MECHANISM AND SIGNIFICANCE

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THE abnormal movements of the eyes which are designated "nystagmus" are observed rather frequently. They are of many different types and are seen in many varying conditions. As yet, there is no universally accepted classification, terminology or clinical interpretation of these abnormal movements. The purpose of this article is to describe some forms of nystagmus which are commonly encountered in medical practice and to discuss their mechanisms and significance.

Nystagmus consists of a rhythmic alternating tremor of the eyes. This tremor appears in various positions of gaze, especially the lateral, and usually shows a slow and a fast or quick component, the slow motion being followed regularly and rhythmically by a fast motion in the opposite direction. The direction of the nystagmus is designated by the direction of the fast component; thus, if the fast component is to the right, the nystagmus is described as "nystagmus to the right". The tremor often has a frequency of about 2 to 3 per second, but varies markedly in rate. Although spontaneous nystagmus may be seen in normal individuals, it is more frequently a sign of ocular or systemic disease[17].

In the examination for nystagmus, the patient fixes his gaze on the examiner's finger which is held 45 degrees to the left, then to the right, then above, then below the patient's eyes for a few seconds at a time. The patient is then instructed to stare directly forward, since nystagmus may be seen in this position of the eyes in disease of the brain stem. If nystagmus is suspected but not readily apparent, observation of a blood vessel in the conjunctiva is helpful. On studying the optic disc with the ophthalmoscope, nystagmus on direct forward gaze is more easily seen, since the disc and its motion become magnified by approximately 6 times. Convex lenses of 4 to 20 diopters held before the patient's eyes will both diminish fixation and render nystagmus more apparent in any position of gaze.

Laboratory techniques for observing nystagmus include motion picture study, the use of the brain wave appa-

ratus[37], the use of the corneal microscope or slit lamp and direct recording of motions of the eye by attachment of a kymograph lever to an anesthetised area of the cornea.

Associated Phenomena. Various subjective symptoms may accompany nystagmus; oscillopsia, or the visual illusion in which stationary objects seem to move, is one[8]. Oscillopsia accompanies nystagmus of recent origin. The visual sensation of movement is in the same direction as the nystagmus. Blurring of vision is also noted and, rarely, a patient complains of distortion in the form of objects[4]. Vertigo and nausea accompanying nystagmus are well known. Some persons are able to report the onset of their own nystagmus and accurately estimate the changes in amplitude of the movements[25].

Objective findings of many sorts may accompany nystagmus. The patient may fall to either side or in an anteroposterior direction, or may merely lose his balance. Past pointing and other signs of cerebellar dysfunction are encountered more often than are autonomic phenomena such as sweating, pallor and fall in blood pressure[48]. A comparable tremor of other parts of the body may accompany nystagmus. In the syndrome of myoclonus of the palate, there may be nystagmus, a tremor of facial muscles and a tremor of the palate, with all movements occurring at the same frequency[28]. The tremor of the palate is occasionally referred to as "palatal nystagmus"[15]. In hereditary familial tremor, nystagmus may accompany tremor of the extremities[14].

Classification of Nystagmus. Classification of nystagmus may be made from many different points of view. In *pendular* nystagmus the oscillations in either direction are approximately equal in rate while in *jerk* nystagmus the oscillations differ markedly in rate, there being a fast or quick and a slow component. In nystagmus of the 1st degree, nystagmus appears only on conjugate gaze to the side of the quick component; in nystagmus of the 2nd degree, there is nystagmus on gaze toward the side of the quick component and on direct forward gaze as well; and in nystagmus of the 3rd degree, there is nystagmus on direct forward gaze and on gaze toward the side of both the quick and slow components. On the basis of etiology, nystagmus may be classified as neurogenic, labyrinthine, and ocular. A more elaborate classification is that of de Jong[29]:

A. Induced Nystagmus. 1. Optokinetic; 2. Labyrinthine: a, rotational; b, caloric; c, galvanic; d, compression; 3. Reflex acoustic; 4. Reflex sensory; 5. Chemical and toxic.

B. Pathologic Nystagmus. 1. Ocular: a, optic deviation; b, occupational; c, spasmus nutans; d, reflex: 1) With painful disease of the eye; 2) Neuromuscular: a) paretic; b) fatigue; c) eccentric fixation; d) latent nystagmus; 2. Nystagmus due to disorder of centers controlling ocular movement and equilibrium: a, vestibular nucleus; b, cerebellum; c, cerebral oculogyric areas; d, cervical spinal cord; 3. Miscellaneous: Toxic, congenital, voluntary, and hysterical.

It should be noted that the author of an extensive classification of nystagmus states that "any classification of nystagmus is open to criticism as it must be somewhat arbitrary and subject to exceptions"[29].

Types of Nystagmus. *Uniocular nystagmus.* Nystagmus is usually present in both eyes at once, but it may appear in one eye only, although both eyes be uncovered. This uniocular nystagmus appears in tetany of the newborn[2], in multiple sclerosis, in congenital facial hemiatrophy[51], and in spasmus nutans. Spasmus nutans is seen in infants under 2 years of age; it is

characterized by a tremor in which the head rotates upon the neck while the eyes look forward in the antero-posterior axis of the body, and by pendular nystagmus which may be uniocular and usually is of different grade in the two eyes. These signs usually disappear by the age of 3[22]. Uniocular nystagmus is also said to occur in an eye with optic nerve atrophy[29].

Latent nystagmus may appear only when one or both eyes are covered. This usually accompanies poor visual acuity in one or both eyes. In latent nystagmus, covering one eye produces nystagmus in both eyes, only exceptional cases showing uniocular nystagmus. Latent nystagmus becomes manifest on rendering unequal either the brightness or the distinctness of the visual image in the two eyes[11]. Some varieties of nystagmus persist when the eyes are voluntarily closed. The tremor of the eyes may then be seen and palpated through the closed lids, and even heard through the bell of a stethoscope[19,25].

Positional nystagmus occurs with changes in position of the entire body, or of the position of the head upon the neck[35]. In tumors of the posterior intracranial fossa, tilting the head back may produce headache, vertigo, and nystagmus. Parasites floating free in the fourth ventricle may also cause this rather rare response to retraction of the head[7]. In some cases of postural vertigo, if the individual lies back quickly with his head turned toward one shoulder, usually the right, true vertigo and mixed rotary and vertical nystagmus of vestibular type will develop. In animals, positional nystagmus occurred after cauterization of the midportion of the cerebellum[25].

The *pattern of movements* of the eyes may vary greatly. Nystagmus may be horizontal, or vertical or oblique, the eyes may rotate in clockwise or counterclockwise fashion, or the nystagmus may be a mixture of many combinations of these directions. The movements of the two eyes may be essentially similar (conjugate nystagmus) or may differ (dysconjugate nystagmus). There may be recurrent convergence or divergence spasms, sometimes called convergent and divergent nystagmus; or disjunctive nystagmus; or repetitive retraction of the eyes, described as retractory nystagmus[22]. In another form of disjunctive nystagmus, "see-saw" nystagmus, one eye goes up while the other goes down[39].

Paroxysmal nystagmus is not uncommon. One of us recently observed a girl of 13 with a three month history of petit mal epilepsy, who on being made to overbreathe would have an attack of unconsciousness associated with fast upward nystagmus for four or five seconds. In grand mal epilepsy, sustained deviation of the eyes to one side, or nystagmoid movements, may be a feature of the attack. The syndrome of "migraine otique", characterized by headache, vertigo, tinnitus, visual field defects and nystagmus, may come in paroxysms[2]. Nystagmus may accompany possible vasospasm of the brain stem as was postulated in the following case: a 26 year old physician who is quite healthy except for recurrent attacks of diarrhea which follow ingestion of tuna fish, ate some pickled herring of excellent flavor but of unknown quality. Within 30 minutes he had diarrhea, projectile vomiting and rotary nystagmus as he looked directly forward. There was rotary oscillopsia, in which buildings seemed to tip slowly to the right and rapidly return to the vertical position. He staggered to the right. He was able to retain a tablet of nicotinic acid, 100 mg., and shortly noted flushing of the face. The nystagmus and oscillopsia ceased immediately; the bowel symptoms disappeared within an hour.

In an individual subject with nys-

tagmus, the movements vary from time to time without artificial stimulation. Persons with idiopathic congenital nystagmus show a decrease in the amplitude of the tremor when they are in a state of relaxation; with excitement the tremor becomes more apparent. In most cases, closing the eyes abolishes the nystagmus. If, however, it persists with the eyes closed, sleep may put an end to the movements. Just as other bodily phenomena fluctuate in intensity and quality, nystagmus fluctuates from day to day, even to the point of disappearance.

NYSTAGMUS WITHOUT OBVIOUS DISEASE. Nystagmus is seen in normal persons. Tiny movements of the eyes, too small to be seen without magnification, are part of the normal process of visual fixation[17]. So-called "fixation nystagmus" is caused by fixing the eyes intently on some object at rest. It is involuntary. Nystagmus which appears when the gaze is directed far to one side or the other, so that both eyes cannot fixate the same object at once, is seen in clinically normal subjects. This may be called physiologic neuromuscular nystagmus. Congenital nystagmus, present since birth in those who are otherwise well, is not uncommon. Familial hereditary nystagmus is a relatively rare condition in which the movements appear at birth or shortly thereafter. It is sex-linked and is found usually only in males. In some families, however, the females also have nystagmus[40]. The general health of all members of the family is good[1,38].

Voluntary nystagmus is a medical curiosity in which an individual can cause the eyes to make extremely rapid and fine oscillations at will. These movements are pendular in type and tetanic in nature[11]. A striking instance of this phenomenon was seen in a physician whose vision fell from 20/20 to less than 5/200 in both eyes during the voluntary nystagmus. Hysterical nystagmus, in the absence of organic disease of the brain, labyrinths or eyes, is extremely rare.

INDUCED NYSTAGMUS. Nystagmus may be induced by physical methods in normal subjects. Optokinetic nystagmus ("picket fence nystagmus", "railway nystagmus" or "train nystagmus") is produced experimentally by rotating a striped drum before the eyes. A large lampshade or open cylinder about 24 inches in diameter, painted both inside and out with alternate black and white stripes, has been used. The drum is held a convenient distance away from the patient, who concentrates on the drum while it is rotated at a rate of 2 per second. However, if the patient cannot concentrate satisfactorily, one places the drum over the patient's head and rotates it in this position. This latter maneuver has resulted in nystagmus in most patients tested.

Optokinetic nystagmus is said to require "visual attention"[11]. However, optokinetic nystagmus may be produced in comatose adult patients and anencephalic infants[36] and in animals or humans after removal of one or both cerebral hemispheres, all being cases in which visual attention would presumably be defective or absent. In human subjects, defects in attention have been suggested as the cause of various types of visual field losses[11] but only a small part of the total visual field need be intact to produce normal optokinetic nystagmus[23]. The importance of visual attention in optic mechanisms has been seriously questioned[6]. Two different forms of optokinetic nystagmus have been described—"seeing" optokinetic nystagmus, which is said to require the function of the occipital lobes, and "staring" optokinetic nystagmus, said to require the integrity of the superior colliculi[46]. At present, because of insufficient knowledge of the pathways requisite for the production of optokinetic nystagmus,

its absence in a particular case cannot be considered to be of definite localizing value, though it may suggest a lesion of the efferent visual pathways from the occipital lobe to the nuclei of the ocular muscles[11].

Rotational nystagmus follows rotating a subject in the revolving chair of Barany, usually 10 times over a period of 20 seconds. *Caloric nystagmus* is produced by stimulation of the labyrinth, running either cool or warm water or alcohol vapor into one or both external auditory canals. A simple technique for caloric stimulation of the semicircular canals consists in the irrigation of one external auditory meatus with 100 cc. of cool water drawn from the tap, with the patient sitting erect. *Galvanic nystagmus* is produced by running a current of about 2 milliamperes between the 2 mastoid processes[16]. These forms of induced nystagmus may also be induced in patients with pathological nystagmus, causing changes in the rate and direction of the abnormal ocular movements. In patients with fistulous disease of the middle ear compression of the air column within the external auditory meatus may produce nystagmus[21].

Nystagmus in Disease of the Central Nervous System. Nystagmus is a feature of many diseases involving the central nervous system. Lesions associated with nystagmus are seen in the brain stem in general and in the middle portion of the medulla in particular, principally in the zone between the vestibular and the oculomotor nuclei[29]. Involvement of the tracts which enter the vestibular nuclei is a common finding. Lesions of the cervical spinal cord[45], of the midline portion of the under surface of the cerebellum, and of the adversive eye fields of the cerebral hemispheres (in the middle frontal gyrus, temporal and occipital lobes) have all been found[36].

The physiologic mechanism by which these lesions cause nystagmus has not yet been settled. It is known that the 2 vestibular nuclei are in steady tonic equilibrium, each nucleus tending to turn the head and eyes toward the opposite side[32,50]. Synergistic relationship between the prefrontal adversive areas and the cervical spinal cord have been found necessary to produce conjugate eye movement[10]. The slow component of nystagmus has been shown to follow derangement of the vestibular nucleus, and evidence has been adduced to show that the mechanisms for production of the fast component originates in this structure, or in the reticular substance of the medulla[29]. In persons who have been blind since birth, the fast phase is not prominent.

Nystagmus persists for long periods after cessation of a nystagmogenic stimulus[34]. The concept of a reverberating neuronal circuit has been proposed to explain the persistence of the alternating movements in nystagmus[25,32].

Peripheral neuromuscular mechanisms which are involved in eye movements differ from mechanisms of movement found elsewhere in the body. Proprioceptive sense is absent in the human eye[11]. Antagonistic muscles of the eye relax when agonists contract, just as in other muscles of the body. Stretching of an extraocular muscle will, however, produce nystagmus[44], while stretching of a muscle in an extremity produces a single set of movements, similar to the patellar tendon reflex. Microscopic examination confined to the bellies of extraocular muscles has led to the belief that the human being has no muscle spindles in these muscles, but recent study of their insertions reveals the presence of characteristic muscle spindles. Their muscle bundles are small and they possess a relatively small number of neuromuscular spindles which are the afferent end organs concerned in stretch reflexes[12]. However, grapelike endings of proprio-

ceptive afferent nerves ("terminaisons en grappe") are readily found in the ocular muscles[33]. These latter structures have their central neuronal connections in the region of the oculomotor nuclei[13].

Among the neurological diseases in which nystagmus is seen, multiple sclerosis takes a prominent place. Although many signs and symptoms of multiple sclerosis are subject to remission and exacerbation, nystagmus in this disease seldom disappears. The nystagmus tends to be unevenly conjugate or dissociated; that is, on lateral gaze, there is a difference in amplitude of nystagmus in the two eyes. The abducting eye may show coarse nystagmus while the adducting eye shows internal rectus weakness[5]. In Friedreich's ataxia, nystagmus is often a prominent feature of the clinical picture. We have studied a patient with this latter disease who showed nystagmus which alternated spontaneously from one side to another for over a year of observation[25]. Nystagmus appears in the neuropathies and in syringobulbia.

In nystagmus due to disease of the central nervous system, the direction of the fast component usually changes with the direction of gaze. The intensity and duration of nystagmus is of lateralizing value in neurological diagnosis. The lesion is generally on the side toward which the amplitude is the greater. Vertical nystagmus indicates the presence of disease of the brain stem. Nystagmus due to disease of the brain generally shows a fast and slow component, but tremors of the extremities due to cerebral causes are usually pendular in pattern.

Labyrinthine Nystagmus. Disease of the labyrinths can produce nystagmus for a short period of time. After destruction of one labyrinth, nystagmus to the opposite side appears and persists for 2 or 3 days; it usually disappears within a week[31]. Associated with labyrinthine nystagmus there may be other signs such as tinnitus, falling, deafness and failure of the affected labyrinth to respond to stimulation. In labyrinthine nystagmus, the direction of the fast component does not change with change in the direction of gaze.

The study of induced labyrinthine nystagmus is of value in the diagnosis of lesions of the 8th nerve and of the labyrinthine system. In health, the duration and intensity of induced nystagmus to the left and right are equal. Inability to elicit nystagmus by stimulation of the labyrinth on one side ("sign of a dead labyrinth") is of localizing value in diagnosis. In tumors of the cerebellopontine angle, the function of the horizontal semicircular canal on the affected side is lost, as is function of the vertical canal of the opposite side[9].

The labyrinths are not essential for the production of nystagmus. On section of the eighth cranial nerve, the head and eyes turn toward the affected side and there is nystagmus to the opposite side. These signs generally disappear after a week. If the other eighth nerve is sectioned after this period, turning of the head and eyes as well as the nystagmus reappear, but all are in reverse directions to those of the previous experiment. This nystagmus persists for 2 or 3 days when both labyrinths are thus cut off from functional communication with the brain stem. Extirpation of one labyrinth and then the other, produces similar results. Galvanic nystagmus can be produced in an animal without labyrinths[31].

Ocular Nystagmus. In ocular or "searching" nystagmus, the movements of the eyes are pendular in type. The eyes wander slowly to and fro, the excursion to each direction being approximately equal in rate, although the excursions vary greatly in rate in individual cases. This type of nystagmus

is associated with poor fixation of an optical image upon the macula. It is seen in individuals with extremely poor visual acuity, albinism, aniridia, severe astigmatism, deficient color vision, and occasionally with severe photophobia. Miner's nystagmus appears when the amount of light at the coal face falls below 0.4 foot candles, a condition which is not found in this country[43].

Weakness of the extraocular muscles is frequently given as a cause of nystagmus[18]. Such weakness is present in myasthenia gravis, producing ptosis, diplopia and squint. Yet in untreated and treated patients with myasthenia gravis we have not been able to elicit nystagmus on voluntary gaze in any direction. In 3 untreated myasthenics recently observed, nystagmus in the horizontal and vertical planes was produced by means of an optokinetic drum. This nystagmus was continuously induced over a 2 minute period, at the end of which there was some diminution in amplitude and evenness of ocular excursion, suggesting ocular fatigue. The patients then fixated the examiner's finger in lateral and vertical positions. Nystagmus did not appear. It is clear, then, that weakness of the extraocular muscles did not cause nystagmus. Furthermore, in patients exhibiting weakness of various extraocular muscles due to lesions of the extra medullary portion of the third intracranial nerve, nystagmus is usually not seen.

Nystagmus has been considered a compensatory movement pattern, but actually makes the vision worse[11]. In general, the duration of different types of pathologic nystagmus is as follows: ocular nystagmus persists for years or life; neurogenic nystagmus lasts for months or years; and labyrinthine nystagmus for days or weeks[31].

Nystagmus Due to Drugs. The drugs which cause nystagmus most commonly are the barbiturates. Amobarbital, pentobarbital, and phenobarbital when taken by mouth in large doses produce nystagmus. If the amount of drug has been sufficient to result in coma, as in an attempt at suicide, nystagmus is usually present. Much smaller doses of barbiturates are required to produce nystagmus when they are given by vein. The speed of the injection is a factor in that slow injection is less likely to produce the ocular movements. Intramuscular injection is intermediate in effectiveness between oral and intravenous administration. When giving pentobarbital or amobarbital intravenously at the slow rate often used in psychiatric interviews (0.1 gm. per minute) nystagmus appears in most persons after about 0.2 gm. have been injected. By the oral or intramuscular route 1.0 gm. is often required. Nystagmus on lateral gaze appears first, with smaller doses of the drug, and disappears last. Nystagmus on vertical gaze requires larger amounts of drug and disappears earlier. Before nystagmus on direct forward gaze takes place, massive dosage must be administered, resulting in unconsciousness.

Yet in patients who have nystagmus on direct forward gaze from many causes besides drug intoxication, small amounts of barbiturates by vein will abolish the nystagmus. As little as 0.1 gm. of sodium amobarbital abolished the nystagmus for a brief period in a patient with congenital nystagmus, while a smaller dose gave the same result in a patient with alcoholic encephaloneuropathy. The reason for this is unknown. The visual acuity improves when the nystagmus is abolished by any mechanism.

Another drug which produces nystagmus is ethyl alcohol. Acute and moderately heavy intoxication with alcohol, whether given by mouth or intravenously, is associated with nystagmus. Chronic alcoholism, when accom-

panied by signs of diffuse disorder in the nervous system, as in delirium tremens, may present nystagmus as part of the clinical picture[24]. It is interesting to note that 2 alcoholic patients with encephalopathy and vertical nystagmus on direct forward gaze completely lost this nystagmus for a brief period when alcohol was administered.

Hydantoinates (*e. g.*, dilantin), so often used in the treatment of epilepsy, can produce nystagmus. In hydantoin intoxication, nystagmus often appears as the first sign of intoxication. This is in contradistinction to barbiturate toxicity, in which many other clinical signs appear earlier than nystagmus. In the treatment of epilepsy, both barbiturates and hydantoins are combined to good effect, but insofar as nystagmus is concerned, we have not observed a synergistic effect involving the 2 drugs. The appearance of nystagmus during treatment of epilepsy with these drugs does not call for their withdrawal.

Curare in small doses (20 to 40 units intravenously) will produce nystagmus on lateral gaze. With larger doses (above 60 units intravenously) nystagmus on vertical gaze appears, followed by ptosis, flattening of the facies and complete paralysis of the movements of the eyeballs. Although intravenous injection of mephanésin, a synthetic curare-like drug (tolserol, oranixon) results in nystagmus, oral administration of this drug in dosage up to 3 gm. daily did not produce this effect[42].

REFERENCES

(1) **Allen, M.**: J. Hered., **33**, 454, 1942.

(2) **Bakwin, H.**: Revue Franç. de Ped., **10**, 3, 1934. (3) **Bender, M. B.**, and **Furlow, L. T.**: Arch. Neurol. and Psychiat., **53**, 29, 1945. (4) **Bender, M. B.**, and **Gorman, W. F.**: Am. J. Ophth., **32**, 967, 1949. (5) **Bender, M. B.**, and **Weinstein, E. A.**: Arch. Ophth., **21**, 266, 1939. (6) **Bender, M. B.**, **Wortis, S. B.**, and **Cramer, J.**: Arch. Neurol. and Psychiat., **59**, 273, 1948. (7) **Biggert, J. H.**: Pathology of the Nervous System, p. 135, Baltimore, Williams & Wilkins, 1940. (8) **Brickner, R. M.**: Arch. Neurol. and Psychiat., **36**, 586, 1936. (9) **Brock, S.**: Basis of Clinical Neurology, p. 194, Baltimore, Williams & Wilkins, 1945.

(10) **Claes, E.**: Arch. Int. de Physiol., **48**, 238, 1939. (Cited by Spiegel, E. A.[47]). (11) **Cogan, D. G.**: Neurology of the Ocular Muscles, p. 127, Springfield, Ill., Charles C Thomas, 1949. (12) **Cooper, S.**, and **Daniel, P. M.**: Brain, **72**, 1, 1949. (13) **Corbin, K. B.**, and **Harrison, F.**: J. Comp. Neurol., **77**, 171, 1942. (14) **Critchley, M.**: Brain, **72**, 113, 1949.

(15) **Davidson, C.**, **Riley, H. A.**, and **Brock, S.**: Bull. Neur. Inst. of N. Y., **5**, 000, 1936. (16) **Dix, M. R.**, **Hallpike, C. S.**, and **Harrison, M. S.**: Brain, **72**, 241, 1949. (17) **Duke-Elder, W. S.**: Textbook of Ophthalmology, p. 629, St. Louis, C. V. Mosby, 1937. (18) Idem: Ibid., p. 50.

(19) **Fenn, W. O.**, and **Hursch, J. B.**: Am. J. Physiol., **118**, 8, 1937. (20) **Fischer, J. J.**: New England J. Med., **4**, 142, 1949. (21) **Fisher, J.**, and **Wolfson, E.**: The Inner Ear, p. 86, New York, Grune & Stratton, 1943. (22) **Ford, F. R.**: Diseases of the Nervous System in Infancy, Childhood and Adolescence, p. 1076, Springfield, Ill., Charles C Thomas, 1945. (23) **Fox, J. C.**, and **Holmes, G.**: Brain, **49**, 333, 1926.

(24) **Gorman, W. F.**: The Interne, **6**, 152, 1949. (25) **Gorman, W. F.**, and **Brock, S.**: Am. J. Ophth. To be published.

(26) **Harris, W.**: Brit. J. Ophth., **28**, 40, 1944. (27) **Huizinga, E.**: Acta Otolaryng., **15**, 451, 1931.

(28) **Jacobson, M. B.**, and **Gorman, W. F.**: Arch. Neurol. and Psychiat., **62**, 798, 1949. (29) **DeJong, R.**: Arch. Neurol. and Psychiat., **55**, 43, 1946.

(30) **Kestenbaum, A.**: Critical Methods of Neuro-Ophthalmological Examination, p. 250, New York, Grune & Stratton, 1946. (31) **de Kleyn, A.**: Confinia Neurol., **2**, 257, 1939.

(32) **Lorente de No, R.**: Trans. Am. Otol. Soc., **22**, 287, 1932.

(33) **Maximow, A. A.**, and **Bloom, W.**: A Textbook of Histology, p. 199, fig. 176, Philadelphia, W. B. Saunders Co., 1948. (34) **Mowrer, O. H.**: Science, **81**, 180, 1935. (Cited by Spiegel, E. A.[47].)

(35) **Nylen, C. O.:** Acta Otolaryngol., Supp. **15,** 1, 1931.

(36) **Rademaker, G. G. J.,** and **Ter Braak, J. W. G.:** Brain, **71,** 59, 1948. (37) **Redlich, F. C., Callahan, A.,** and **Schmidjye, J. F.:** Yale J. Biol. and Med., **18,** 269, 1946. (38) **Rucker, C. W.:** Am. J. Ophth., **29,** 1534, 1946. (39) Idem: Arch. Ophth., **35,** 301, 1946. (40) Idem: Am. J. Human Genetics, **1,** 52, 1949.

(41) **Scala, N. P.,** and **Spiegel, E. A.:** Conf. Neurol., **3,** 53, 1940. (42) **Schlesinger, E. B., Drew, A. L.,** and **Wood, B.:** Am. J. Med., **4,** 365, 1948. (43) **Sharpley, F. W.:** Brit. J. Ophth., **20,** 129, 1936. (44) **Sherrington, C. S.:** Proc. Roy. Soc., **53,** 407, 1933. (45) **Smith, H. C.,** and **Riesenman, F. F.:** Arch. Ophth., **33,** 13, 1945. (46) **Spiegel, E. A.:** Conf. Neurol., **3,** 191, 1941. (47) **Spiegel, E. A.,** and **Sommer, I.:** Neurology of the Eye, Ear, Nose and Throat, p. 116. New York, Grune & Stratton, 1944. (48) Idem: Ibid., p. 147. (49) Idem: Ibid., p. 160. (50) Idem: Ibid., p. 164. (51) **Spiller, W. G.:** Brain, **47,** 345, 1924.

(52) **Walsh, F. B.:** Clinical Neuro-Ophthalmology, p. 461, Baltimore, Williams & Wilkins, 1947.

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BOOK REVIEWS AND NOTICES

THE 1949 YEAR BOOK OF GENERAL SURGERY. Edited by EVARTS A. GRAHAM, M.D. Pp. 707; 216 ills. Chicago: Year Book Publishers, 1950. Price, $4.75.

THIS volume is a collection of synopses of selected papers published in the field of general surgery during the period August, 1948, to July, 1949. The synopses maintain a high standard in that they are brief, clearly written and, above all, factual. The volume affords much of the same saving in time that does reading the summary and conclusions of a series of scientific papers. It goes beyond this, however, in containing only papers which are regarded as of substantial value. Thus many papers are omitted from consideration entirely. It also has the advantage of a valuable index which permits the reader to find and assimilate an outline of recorded progress on most subjects of surgical interest within a very few minutes.

The reader of any synopsis must, of course, realize that the original paper has to be consulted wherever it is essential for him to form an independent critical judgement of the worth of the contribution. This is one of the best of the Year Book series and should be a valuable aid to all who use it with this unavoidable limitation in mind. J. R.

CURRENT THERAPY 1950. Edited by HOWARD F. CONN, M.D., *et al.* Pp. 736. Phila.: W. B. Saunders, 1950. Price, $10.00.

THE current (2d) appearance of this book, under the supervision of 12 consultants and including 267 contributors, has maintained its promise of timely therapy. More conditions are discussed this year; the 14 sections have been increased by 1. Treatment and management are usually discussed by more than 1 contributor—the reader has a choice. One section, devoted to the treatment of acute poisoning, is well devised except for the omission of the modern antidotal treatment of cyanide poisoning. The newer drugs are extensively covered, although if the Editor were to add an additional section they could be appraised as a group on their indications, limitations and future promise.

The format is unchanged, which makes the book easy to consult and read. This is achieved, however, at the expense of size and weight. The completeness of the index makes all information readily available. There are no illustrations but there are informative tables and charts as well as many prescriptions. Here, in a single book, one will find up-to-date therapy and fully current progress. R.G.

THE CYTOLOGIC DIAGNOSIS OF CANCER. By the STAFF OF THE VINCENT MEMORIAL LABORATORY, Boston. Pp. 229; 153 ills.; 30 color plates. Phila.: W. B. Saunders, 1950. Price, $6.50.

THIS manual should be greeted with enthusiasm by all those interested in diagnosing cancer by the cytologic method. It presents, in a detailed and systematic manner, copiously illustrated, the criteria that identify the various cells, including cancer cells, encountered in smears of vaginal secretions, sputum, gastric washings, urine, and exudates from the serous cavities. The lack of sharpness of many of the high-power photomicrographs is well offset by the technique of illustrating each cell type and its variants with a high magnification drawing, as well as both low and high power, photomicrographs. Both diagnosis and cell classification may seem over-simplified to a pathologist, but the Authors' objective of characterizing only the typical was, no doubt, wisely chosen. The manual should be most useful to the inexperienced in cytology. A chapter on technique and a complete bibliography further enhance the value of the book. R. H.

CORONARY CIRCULATION IN HEALTH AND DISEASE. By DONALD E. GREGG, M.D., Chief Research Physician, Med. Dept., Fort Knox. Pp. 227; 73 ills. Phila.: Lea & Febiger, 1950. Price, $4.50.

THE book has chapters on cardiac anatomy, experimental preparations with a critical discussion of different types of instruments and the flow curves obtained, an evaluation of the determinants of coronary flow, metabolism and work, and the coronary circulation in disease. Each chapter has a well selected bibliography. The text makes easy reading, the illustrations, printing, and paper are excellent.

This volume will be invaluable for workers in the field and will also serve as an excellent reference for the general medical profession. It can be most highly recommended. In recent years knowledge of the coronary circulation has advanced rapidly. The complexity of the techniques used has made evaluation of the results difficult, even for those with some knowledge of the field. Dr. Gregg, an eminent investigator, is well qualified by personal experience to speak with authority. Here is a timely and top-notch monograph by a top-notch man. W. S.

THE COMPARATIVE ANATOMY AND PHYSIOLOGY OF THE LARYNX. By V. E. NEGUS, M.S., F.R.C.S., King's College Hospital, London. Pp. 230; 191 ills. New York: Grune & Stratton, 1949. Price, $6.50.

THIS book is a rearrangement and condensation of a work published in 1929 under the title "The Mechanism of the Larynx". As such, it is a decided improvement, for the physical proportions of the original edition made it far too large and heavy to be studied with comfort. The basic philosophy of this book is well expressed by the Author in these words: "The study of pure anatomical details would not be of the slightest interest unless the use and function of the various parts were sought for at the same time." The larynxes of numerous species in the animal kingdom, including the human, are described clearly in terms of anatomy, physiology and evolution. A number of new illustrations have been added, some in outline, of various animals whose structures and habits are referred to in the text. For the reader who wishes to delve into the comparative anatomy and physiology of the larynx, this volume may be regarded as definitive. N. F.

NEW BOOKS

Sex Without Fear. By S. A. LEWIN, M.D., and JOHN GILMORE, Ph.D. Pp. 121; 46 ills. New York: Lear Publishers, 1950. Price, $3.00.

Biologisch - Medizinisches Taschenjahrbuch, 1950. Begründet von Prof. Dr. med. VOGEL, Neubearbeitet von Dr. med. HANS HAFERKAMP. Pp. 512. Stuttgart, Germany: Hippokrates-verlag (Marquardt), 1950. Price, D. M. 7.50.

The 1949 Year Book of Neurology, Psychiatry and Neurosurgery. Edited by ROLAND P. MACKAY, M.D., NOLAN D. C. LEWIS, M.D., and PERCIVAL BAILEY, M.D. Pp. 668; 113 ills. Chicago: Year Book Publishers, 1950. Price, $5.00.

THIS book will be useful to specialists in the fields of Neurology, Psychiatry and Neurosurgery more than to specialists in other fields or to general practitioners. As has been the case with previous Year Books in these fields, it includes abstracts on many of the most important contributions that have been made during 1949. W. P.

Einführung in die Innere Medizin. Von Dr. HANS JULIUS WOLF, Univ. Göttingen. Pp. 653; 73 ills. Stuttgart: Georg Thieme, 1949 (imported by Grune & Stratton, 1950). Price, $6.50.

Epidemics in Schools. An Analysis of the Data Collected 1935-1939. By E. A. CHEESEMAN. Pp. 96. Med. Res. Council Spec. Rept. Series 271. London: H. M. Stationery Office, 1950. Price, 3s.

The General Report of the Pharmaceutical Survey, 1946-1949. EDWARD C. ELLIOTT, Director. Pp. 240. Washington, D.C.: American Council on Education, 1950. Price, $6.00.

An educational study that corresponds to similar national surveys undertaken by this Council in medicine, dentistry, law, and other professional fields. An unequalled amount of facts about the profession of pharmacy has been assembled to provide a basis for recommendations leading to the improvement of that profession. E. K.

Infrared Radiation Therapy Sources and the Analysis with Scanner. By LEOPOLD ROVNER, Consulting Physicist, Cambridge, Mass. Pp. 34; 21 figs. Springfield, Ill.: Charles C Thomas, 1950. Price, $1.50.

THE purpose of this study is primarily to clarify the present status of coverage patterns produced by infrared generator equipment. Equipment is described that automatically plots radiation intensity against lateral distance from the axis of the infrared source. The mechanical and electronic aspects of the instrument are described in some detail. The physical validity of the method is discussed, and 10 coverage patterns obtained from various infrared lamps are presented. E. P.

How to Stop Killing Yourself. By PETER J. STEINCROHN, M.D. Pp. 272. New York: Wilfred Funk, 1950. Price, $2.95.

The Autobiography of Wilhelm Stekel, The Life Story of a Pioneer Psychoanalyst. Edited by EMIL A. GUTHEIL, M.D. Pp. 293; 19 ills. New York: Liveright, 1950. Price, $4.00.

THIS is an account of the life of one of Sigmund Freud's eminent disciples. As is pointed out in the preface, it was considerably influenced by Rousseau's "Confessions". The book tells of life in old Vienna and throws light upon an early phase of the psychoanalytic movement. Written during the last few years of Stekel's life when he was ill, it expresses the reasons for Stekel's ending his life voluntarily in London in 1940. It is a significant contribution and will be appreciated by those who are interested in this field. W. P.

The Law of Medicine. By PARNELL CALLAHAN, LL.B., and JUSTIN CALLAHAN, M.D. Pp. 80. New York: Oceana Publications, 1950. Price, $1.00 paper; $2.00 cloth.

THIS brochure contains, in abstract form, a description of the various groupings of the medical arts and the qualifications for the practice of medicine and of nursing in the various States. There is also a guide to the prospective doctor which, if followed, will help him to avoid errors relating to civil and criminal practice. It is a very handy and helpful primer for the embryo physician. F. L.

Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death. In 2 vols. 6th Revision adopted 1948. Pp. 376, 524. Geneva, Switzerland: World Health Organ. Price, $6.00.

THIS 6th revision is the first to provide "a single list applicable to both morbidity and mortality statistics; it defines the content of the individual categories of the Classification . . . represents international agreement on a uniform method of selecting the main cause to be tabulated . . . " The entire 2d volume is an alphabetical index of the diseases listed in Vol. 1, each with its classification number, and preceded by directions on the use of the 2 volumes.

Amusing Quotations for Doctors and Patients. Edited by NOAH D. FABRICANT, M.D. Pp. 149. New York: Grune & Stratton, 1950. Price, $3.00.

"In this book I have tried to gather in readable, convenient form a selection of amusing quotations dealing with various aspects of the medical scene, its mosaic of interests and ramifications . . . some nonsense has been included deliberately, for it is sometimes just as intriguing to detect men's foolishness as it is to observe their sagacity" (Preface). The material, arranged alphabetically by subjects ranging from Accidents to Youth, is followed by a list of authors with their dates, but no page numbers referring to their quotations are included in this entertaining anthology. E. K.

The British Encylopaedia of Medical Practice. Medical Progress, 1950. Edited by RT. HON. LORD HORDER, G.C.V.O., St. Bartholomew's Hospital. Pp. 556. And Cumulative Supplement, 1950. Pp. 481. London: Butterworth & Co., 1950. Price, $14.00.

Simmonds' Disease. By R. F. FARQUHARSON, M.B., F.R.C.P., Prof. of Medicine, Univ. of Toronto. Pp. 93; 5 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.00.

A brief monograph, No. 34 in the American Lecture Series, upon extreme insufficiency of the adenohypophysis, a disease that is now accepted as much commoner, and thus more important, than was long suspected.

Simplified Chemistry Experiments. By ARMAND JOSEPH COURCHAINE, Instructor in Biological Chemistry, Hahnemann Med. Coll., Phila. Pp. 234; 13 ills. New York: G. P. Putnam's Sons, 1950. Price, $2.80.

The Physiology of Thought. By HAROLD BAILEY, M.D. Pp. 313. New York: William-Frederick Press, 1949. Price, $3.75.

Training for Childbirth. By HERBERT THOMS, M.D., Prof. of Obstetrics and Gynecology, Yale Univ. School of Med. Pp. 114; 14 ills. New York: McGraw-Hill, 1950. Price, $3.00.

A lucid and sensible discussion of a timely subject. We are glad to have printed Dr. Thoms' article on Natural Childbirth in this journal 219, 679, 1950.

NEW EDITIONS

Textbook of Biochemistry. By BENJAMIN HARROW, Ph.D., Prof. of Chemistry, City College of New York. 5th ed. Pp. 609; 139 figs. Phila.: W. B. Saunders, 1950. Price, $6.00.

IN a field that changes month by month no textbook can be really up to date at the time it is published. Nevertheless, Dr. Harrow's revision of his popular text and his selection of recent work for inclusion is an excellent achievement. Material on biological antagonists, micro-biological assay, photosynthesis, antibiotics, and paper chromatography has been added. The references are a well chosen coverage of the literature through 1949. The important chapters on enzymes and intermediary metabolism are adequate from the aspect of information presented, though clarity has sometimes been sacrificed for brevity in the presentation of these difficult subjects. From the student's point of view, these chapters could profitably be expanded at the expense of the less complicated material on respiration and foods. M. B.

Medicine of the Year, 1950. Edited by JOHN B. YOUMANS, M.D., Dean, School of Medicine, Vanderbilt Univ. Pp. 204. Phila.: J. B. Lippincott, 1950. Price, $5.00.

THIS is the second year that this review has been published. The list of editors and authors of the reviews is impressive. Each section is necessarily brief, even sketchy, but the bibliography will be a guide to those seeking fuller information on recent advances in their fields of interest. E. R.

Manual of Bandaging, Strapping and Splinting. By AUGUSTUS THORNDIKE, M.D., Assoc. in Surg., Harvard Med. School. 2d ed. Pp. 148; 119 ills. Phila.: Lea & Febiger, 1950. Price, $2.00.

THIS little manual will no doubt continue to be useful to the student and intern as a guide to the proper application of bandages and splints. It is simple and direct with uncomplicated line drawings to guide the inexperienced. E. R.

Treatment in Psychiatry. By OSKAR DIETHELM, M.D., Prof. of Psychiatry, Cornell Univ. Med. Coll. 2d ed. Pp. 574. Springfield, Ill.: Charles C Thomas, 1950. Price, $8.50.

THIS is a valuable text or reference book for the Psychiatrist. Completely rewritten, it contains a wealth of information about therapy. Many developments are covered which have occurred in the field since the 1st edition appeared 14 years ago. W. P.

A Primer for Diabetic Patients. By RUSSELL M. WILDER, M.D., Mayo Foundation. 9th ed. Pp. 200; 8 figs. Phila.: W. B. Saunders, 1950. Price, $2.25.

The Merck Manual of Diagnosis and Therapy. 8th ed. Pp. 1592. Rahway, N. J.: Merck & Co., 1950. Price, regular ed., $4.50; thumb-index ed., $5.00.

"This Golden Anniversary edition exceeds all previous editions in scope." For convenience as a "ready reference" it is, as usual, unexcelled.